IODINATED TYROSINES IN THE PLASMA OF PATIENTS WITH THYROTOXICOSIS

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IT is now nearly ten years since radioactive iodine was first used in this country for the treatment of thyrotoxicosis, and it has been in use in the U.S.A. for nearly twice as long. Nevertheless, the results of treatment are still far from satisfactory, and are unpredictable in the individual case.

The possibility that there are two distinct types of thyroid disorder has been put forward many times. Plummer in 1928 suggested that exophthalmic goitre (Graves' disease) and thyrotoxic adenomatous goitre were distinct entities, and that in exophthalmic goitre (which is characterised by hyperplasia of the entire gland) two thyroid products were produced—the normal hormone, and one which was incompletely iodinated and therefore toxic. In the adenomatous goitre the normal hormone was produced to excess. This has not been proved, but the investigation has been intensified, using radioactive isotopes and modern chemical technique, such as chromatography and electrophoresis.

There is now general agreement that the plasma of thyrotoxic patients contains thyroxine, triiodothyronine, and iodide, but there is still some controversy about the presence or absence of iodinated tyrosines—though these have been identified after therapeutic amounts of radioactive iodine, and have been attributed to the effects of the irradiation (Brown and Jackson 1954). Abbatt and Farran (1956) found that iodinated tyrosines were sometimes, but not always, detectable in small amounts in the plasma of thyrotoxic patients before, as well as after, treatment.

A number of teams have now published the results of radioactive iodine therapy. As a general rule 50–60% of the patients become euthyroid after one treatment, and a further 20–30% after repeated treatments. 10–20% develop myxœdema which is probably permanent (Blomfield et al. 1955, Chapman and Maloof 1955, Larsson 1955, Macgregor 1957). There is no dispute that patients with large glands require a higher radiation dose per gramme of tissue to restore them to a euthyroid state, but no explanation of this has been suggested.

Material and Methods

Between October, 1955, and the end of 1957, 118 treatments with radioactive iodine were given to 108 thyrotoxic patients at New End Hospital.

They were more than 45 years of age or unsuitable for surgery because of (1) recurrent thyrotoxicosis, (2) heart-disease, whether connected with the thyroid state or not, (3) an impalpable thyroid, or (4) other indications. Inevitably the series is a selected one, and contains a high proportion of patients with thyrotoxicosis which has either not responded to other methods of treatment or is associated with concurrent disease. No standardised anti-thyroid drug preparation was given before treatment, but in most cases carbimazole 10 mg. t.d.s. was given until patients were admitted to hospital for the radioactive iodine therapy. Many patients were referred from other hospitals specifically for ^{131}I therapy after courses of treatment with the various anti-thyroid drugs.

In 92 of these patients a detailed study has been made of the radioactive constituents of plasma samples, which were taken as a routine 48 hours after the administration of the therapeutic dose of radioactive iodine.

The activity of the separated plasma was measured, and the amount of labelled protein-bound iodine estimated after precipitation of the proteins with trichloracetic acid. This activity is expressed as the percentage of the administered dose which is present as protein-bound ^{131}I in a litre of plasma. The activity of the fraction of the plasma which was extractable with n-butyl alcohol was measured, and its composition studied by means of two-dimensional chromatography, using butanol-ethanol-ammonia and butanol-acetic acid as described by Farran, Parker, and Abbatt (1957). Since the beginning of 1957 the activity of a tracer dose given during the week immediately preceding treatment has been increased to 200 μC; and chromatograms have been prepared from butanol extracts of plasma taken 48 hours after the administration of this tracer dose. In the majority of cases the tentative estimation of the presence or absence of iodinated derivatives, made from the first chromatograms, was confirmed when the chromatograms following therapy were studied independently by a different member of the team.

The type of gland, whether nodular or diffuse, was noted and this observation was usually the independent opinion of two separate clinicians. The size of the thyroid was estimated by palpation, and checked by scanning with a collimated scintillation counter.

In most cases reasonably good agreement was found between the two methods, but it was realised that there may be considerable errors by either method: the clinical method was used throughout in the estimation of the radiation dose which was calculated from the formula

$$E = \frac{15{\cdot}9\ UT}{M}$$

where E = the energy in rads. absorbed by the gland, M = estimated weight of thyroid in grammes, T = effective half-life in days, and U = the effective uptake, which is taken to be the uptake at zero time, and is obtained by extrapolating the half-life curve back to the time of administration.

The radiation dosage given to each patient was based on the estimated size of the gland, and on the findings obtained from a tracer dose of from 50 to 200 μC given at least 48 hours before the treatment. The urinary excretion over 48 hours and the neck uptake at 48 hours were also taken into account; since the beginning of 1957, the effective half-life and effective uptake in the thyroid were used. Three months after treatment the patients were reassessed clinically, by means of an ^{131}I excretion test, and, when practicable, two B.M.R.s. The "T" index (Fraser et al. 1953) was used in the ^{131}I assessment, and the agreement between the value for "T" and the clinical assessment was found to be excellent. The chromatograms were always interpreted by a member of the team having no clinical knowledge of the patient whose blood was under review. Similarly, the clinician making

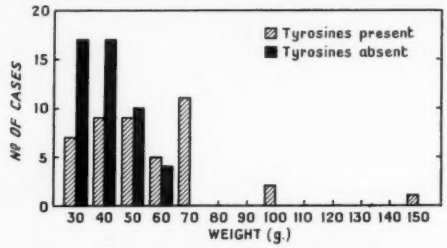

Fig. 1—Weight of thyroid before treatment with ^{131}I.

the three-monthly assessment did not know what had been found in the chromatograms.

Results and Discussion

In 43 of the 92 cases iodinated tyrosines were found in the plasma. The data were analysed to see if any correlations existed between the various characters. The points particularly studied were:

(1) The effects of any previous therapy on (a) the effective uptake in the thyroid; (b) the effective half-life in the thyroid; (c) the results of treatment with radioactive iodine, as measured by "T", three months to a year after treatment; and (d) the presence or absence of iodinated tyrosines in the plasma.

(2) The presence of iodinated tyrosines in the plasma in relation to (a) the effective uptake in the thyroid; (b) the amount of radioactivity given; (c) the presence of exophthalmos; (d) the type of thyroid, nodular or diffuse; (e) the amount of protein-bound iodine in the plasma; (f) the amount of thyroglobulin in the plasma (non-butanol-extractable fraction).

No significant correlations were found between any of these characters, nor between the weight of the thyroid and the effective half-life, nor between the amount of iodinated tyrosines present and the weight of the thyroid.

The group with iodinated tyrosines in the plasma has been compared with the group without these derivatives. Two important differences were found between them—namely, the weight of the thyroid before treatment, and the result of treatment as estimated by "T" (accompanying table and figs. 1, 2, and 3).

Both these differences are highly significant, the probability of their being due to chance being less than 1 in 1000 in each case. Although the difference in the mean weights of the glands in the two groups is highly significant statistically, it is not possible from the thyroid weight alone to decide to which group the patient belongs. It can be seen (fig. 1) that patients whose glands were estimated to be 70 grammes or more all show the presence

STATISTICAL DATA ON THE TWO GROUPS OF PATIENTS

—	Patients with iodinated tyrosines	Patients without iodinated tyrosines	"t"	P
Mean weight of gland before treatment	55 g.	40 g.	3·958	Less than 0·001
Mean value of "T" three months after treatment	21·1	4·0	4·223	Less than 0·001

of iodinated tyrosines. These compounds were found in very few thyrotoxic patients with impalpable glands. It is evident that the patients can be divided into two groups both by the difference in mean value of "T" and by the response as judged by the clinician (fig. 3). These groups are (*a*) those with iodinated tyrosine derivatives in the plasma, with large thyroids, and a poor response to treatment with ^{131}I; and (*b*) those without iodinated tyrosine derivatives in the plasma, with small glands, and a better response to treatment with ^{131}I.

Before attempting to explain these differences, it is necessary to consider why iodinated tyrosines appear in the plasma. The amounts of activity detectable with our present technique depend partly upon the overall activity of the plasma, and partly upon the activity of the iodinated tyrosines, which is seldom greater than 0·03 μC per ml. of plasma, and is usually considerably less. The minimum detectable activity with the technique used is of the order of 0·001μC; iodinated tyrosines have been identified at this level in the plasma, after the administration of 100–200 μC. In these circumstances it seems highly unlikely that the iodinated tyrosines are due to irradiation of the thyroid; but it is not out of the question, nor is it impossible that the substances identified as iodinated tyrosines are artefacts arising from our technique. If they are artefacts they are certainly constant for a particular group of patients. The discrepancies in the literature between those who find iodinated tyrosines in the plasma, and those who can identify only thyroxine, triiodothyronine, and iodine, may well be due to variations in the sensitivity of the methods used. We conclude therefore from our findings that iodinated tyrosines may be present in the plasma of some patients with thyrotoxicosis but are not necessarily a result of irradiation.

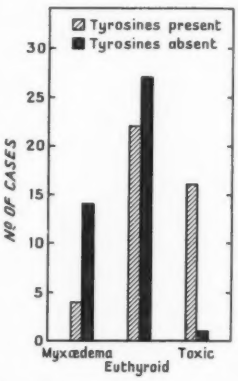

Fig. 3—Result of treatment with ^{131}I (clinical assessment).

Iodinated tyrosines may perhaps be present in all cases of thyrotoxicosis. The amount might vary with the size of the gland, and our technique may or may not be sufficiently sensitive to detect very small amounts of these substances. On the other hand, there may be one or more other unknown factors involved, such as an absolute or relative deficiency of a deiodinating enzyme or dehalo-

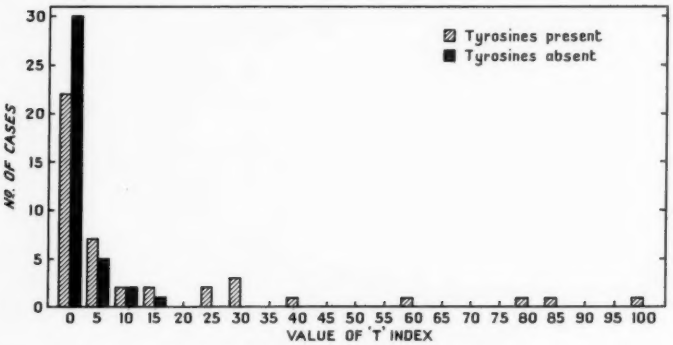

Fig. 2—"T" index after treatment with ^{131}I.

genase. This latter possibility—i.e., abnormal dehalogenation—must remain speculative, since we have no evidence of it from thyrotoxic patients.

An alternative explanation is the one originally put forward by Plummer—namely, that there are two types of thyrotoxicosis. Such a concept would fit the present data. Plummer suggested that exophthalmic goitre and adenomatous goitre with hyperthyroidism were distinct entities, but also stated that in about 20% of his patients with exophthalmic goitre the disease was superimposed on an existing adenomatous goitre; in other words, there was an overlap between the two types. Our data do not support Plummer's classification, in so far as this is based on the recognition of adenomatous and diffuse goitre. However, it is often very difficult to decide on clinical grounds alone which type of goitre is present. As grossly enlarged thyroids are almost always nodular, there must be some association between nodularity and gland size. The highly significant difference in mean gland size in our two groups might therefore be taken as evidence in favour of Plummer's basic hypothesis.

It is generally accepted that in patients who have large goitres disproportionately large amounts of radioactive iodine may be required to control thyrotoxicosis. In our series, patients with large goitres have iodinated tyrosines in the plasma more frequently than patients with small goitres. The cases also show an association between the presence of iodinated tyrosines and the result of treatment by radioactive iodine, as estimated by the " T " factor. The reason for the highly significant difference between the mean values of " T " in the two series is that, of those patients (41 in all) without iodinated tyrosines in the plasma, 13 were finally classified clinically as myxœdematous with only 1 still thyrotoxic. Of those patients (43 in all) with iodinated tyrosines, only 4 were myxœdematous, but 16 were still thyrotoxic. These differences in the clinical results, as was to be expected from the " T " values, are statistically highly significant. All patients who required more than one treatment with radioactive iodine had iodinated tyrosines in their blood.

We are at present unable to explain our results, but from a practical clinical standpoint they seem of considerable importance. Estimation of the presence or absence of iodinated tyrosines makes it possible to select high or low radiation doses respectively for those patients whose thyrotoxicosis is likely to prove " radioresistant " or " radiosensitive ", and who if given too little or too much treatment would remain thyrotoxic or become myxœdematous.

Summary

A preliminary tracer dose of ^{131}I was given to 92 cases of thyrotoxicosis and a detailed study of the radioactive constituents of the plasma was made.

In approximately half the cases (43) iodinated tyrosine derivatives were found in the plasma.

The patients who had iodinated tyrosines in the plasma had also a greater mean gland weight and were more " radioresistant " than those without iodinated tyrosines.

By estimating the iodinated tyrosine derivatives in the blood, patients who will need high doses or low doses of radioactive iodine can be selected.

We are grateful to our clinical colleagues at New End Hospital for their cooperation. We should also like to thank Mrs. Valerie Parker of the M.R.C. Department of Clinical Research, University College Hospital Medical School for technical assistance.

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REFERENCES

Abbatt, J. D., Farran, H. E. A. (1956) *in* Advances in Radiobiology (edited by de Hevesy, Forssberg and Abbatt); p. 305. Edinburgh.
Blomfield, G. N., Jones, J. C., Macgregor, A. G., Miller, H., Wayne, E. J., Weetch, R. S. (1955) *Brit. med. J.* ii, 1223.
Brown, F., Jackson, H. (1954) *Biochem. J.* **56**, 399.
Chapman, E. M., Maloof, F. (1955) *Medicine, Baltimore*, **34**, 261.
Farran, H. E. A., Parker, V., Abbatt, J. D. (1957) *Brit. J. Radiol.* **30**, 445.
Fraser, R., Hobson, Q. J., Arnott, D. G., Emery, E. W. (1953) *Quart. J. Med.* **22**, 99.
Larsson, L. G. (1955) *Acta Radiol. Stockh.* **43**, 126.
Macgregor, A. G. (1957) *Brit. med. J.* i, 492.
Plummer, H. S. (1928) *Trans. Ass. Amer. Phycns.* **43**, 159.

DISSEMINATED LUPUS ERYTHEMATOSUS OF THE ALIMENTARY TRACT

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MORE than sixty years ago Osler (1895) reported eleven cases of erythema exudativum multiforme, in all of which gastrointestinal crises—abdominal colics, usually with vomiting and diarrhœa—were part of the disease.

Material for histological study did not become available in these cases and though in the ensuing half century involvement of the digestive tract in disseminated lupus erythematosus, as the disease became known, was frequently noted, little was known about the pathological basis of the alimentary symptoms. Of 105 cases carefully analysed by Harvey et al. (1954) ulceration of the small intestine with underlying " acute arteritis and thrombosis of small vessels " was observed in 3 instances. In 1 case " the entire intestinal tract was œdematous, many of the small vessels were the site of an arteritis, the mucosa was infiltrated with plasma cells and there were areas of ulceration ". Ileus of the small intestine occurred in 5 of 87 cases reported by Brown et al. (1956) who made a plea for careful necropsy studies in this disease in order to elucidate its mechanism.

The case reported here is unique in the number of intestinal crises and in the opportunity to study the histological findings in the acute phase of an episode and also after death. It emphasises in the natural history of the active disease the long period that may elapse before a diagnosis is established with laboratory precision.

Case-record

On May 21, 1955, a single woman of 27, a book-keeping clerk, was admitted to the Gastro-intestinal Unit as an abdominal emergency. Three days before she had had epigastric discomfort merging slowly into central abdominal colic. Nausea, vomiting, and diarrhœa were associated from the beginning. On the day of admission the pain localised in the right iliac fossa. The only previous history of note was three discrete epileptiform seizures between 1949 and 1951, which did not recur after she started to take phenobarbitone daily.

There was slight fever (100°F) and a raised pulse-rate (97). The white-cell count was 1600 per c.mm. General abdominal tenderness was present, and was maximal in the right iliac fossa. Rebound tenderness was marked and rectal examination showed tenderness in the pouch of Douglas. Bowel sounds were infrequent and poor.

Fig. 1—Follow-through of barium meal in February, 1956, showing spasticity and irregularity of ileum.

A presumptive diagnosis of appendicitis was made and laparotomy was performed. The abdominal cavity contained approximately three pints of clear yellow fluid. Throughout its length the small intestine was diffusely congested, and a few of the mesenteric glands were enlarged and fleshy. The appendix and other viscera appeared normal, but appendicectomy was carried out. Nausea and vomiting continued on the day after operation and gastric aspiration and intravenous fluid and electrolytes were needed. The temperature remained elevated (102°F) and an erythrocyte-sedimentation rate (E.S.R.) of 65 mm. in one hour was noted. Streptomycin (2 g. daily) was given by injection.

By the fifth postoperative day the patient was free from symptoms and seemed well, but an intermittent pyrexia continued until she was discharged on the twenty-second day after operation, and the E.S.R. remained at 100. A Mantoux test was negative to 1/100 dilution, and a barium meal showed slight changes of " instability and minor flocculation of barium in the loops of the small intestine consistent with a diagnosis of non-specific enteritis ". Balance studies showed normal fat excretion.

The day after discharge (June 14) she had to be readmitted. On leaving hospital she took Epsom salts because of backache, and within a few hours had profuse diarrhœa, central abdominal colic, and then repeated vomiting.

The temperature was raised to 99·4°F and the pulse-rate to 110. The abdomen was distended and tender especially in the right iliac fossa, and bowel sounds were absent. Vomiting continued, and hiccups and dehydration necessitated gastric suction and intravenous therapy. The E.S.R. was 63 and the white count 7200. The attack subsided gradually over six days, but even when she was apparently well again the E.S.R. was still 100.

She was kept under observation for a further three weeks. During this period a repeat barium meal showed coarse jejunal mucosa with irregular dilatation of the intestinal loops. The white count fell to 3400, the serum-albumin was low, and there was hyperglobulinæmia, mainly due to elevation of the β-fraction. Repeated blood-cultures and repeated fæcal cultures were negative and all serum-agglutination reactions, including brucella and the Paul-Bunnell tests, were likewise negative. Guineapigs inoculated with the peritoneal fluid removed at laparotomy remained healthy. She was discharged on July 13.

The same evening, two hours after a meal of fried chipped potatoes and pickles, abdominal colic, vomiting, and diarrhœa recurred and she had to be readmitted. The signs were exactly as in previous attacks, but the white count was now 2400. Symptoms subsided in three days on a regime of drip and suction, and eleven days later she was discharged on a maintenance dose of prednisone (75 mg. per day) begun one week before.

She remained symptomless until Jan. 14, 1956, and gained a stone in weight. Then, after a party at which she had consumed much food and alcohol, she was again seized with abdominal colic, vomiting, and diarrhœa, and as these continued for four days she was readmitted. The signs were exactly as before and again she required drip and suction. Anti-histamine (promethazine) was added to the treatment. The white count was 1900, the E.S.R. remained between 50 and 100, and an intermittent pyrexia up to 100°F continued for the next month. An enlarged gland in the right axilla was excised and was reported to show only non-specific hyperplasia of the cells lining the sinuses. Barium meal again showed irregularity and coarsening of the mucosa of the jejunum and ileum, and the terminal ileum had the appearance of Crohn's disease (fig. 1). An aspiration sample of bone-marrow was normal and no lupus-erythematosus (L.E.)-cell phenomena were observed either in the marrow or in the peripheral blood. Wassermann and Kahn reactions were negative. Leucopenia varied in ten successive blood-counts from 1600 to 2600. During this attack the dose of cortisone was increased and a total of 1·5 g. was given over sixteen days. It was by now obvious that the woman was experiencing recurring bouts of fairly acute small-intestine obstruction; and though the pathological cause of the attacks could not be dogmatically stated, the likeliest explanation was some form of regional enteritis.

The uncertainty of the diagnosis and the severity of the attacks were considered to justify operative exploration of the abdomen, and laparotomy was carried out on Feb. 24, 1956.

Free fluid was again present in quantity in the abdominal cavity. The jejenum was grossly abnormal from a point 40 cm. below the duodenojejunal flexure for a distance of 130 cm. The loops were strikingly heavy, intensely congested and of a deep plum colour. The mesentery was congested, and frankly œdematous, and the mesenteric glands were enlarged. Subserous ecchymoses appeared wherever the bowel was handled. Because of the unusual appearance, the bowel wall was incised. It was 1 cm. thick, apparently as a result of gross œdema of the submucosa, and the cut surface exuded watery fluid. The mucous membrane looked normal to the naked eye. At each end of the affected segment there were short transitional zones a few centimetres long before a normal appearance and feel were resumed. A segment 10 cm. long just proximal to the ileocæcal junction showed similar changes. In the abnormal areas the lumen of the intestine was so reduced by the œdematous thickening of the wall that it was virtually non-existent. The rest of the alimentary tract was normal, but it was observed that towards the end of the exploration the subserous vessels throughout the length of the small intestine became markedly dilated and even the previously normal gut wall seemed to swell. A portion of tissue at the site of the jejunal incision and a mesenteric gland were taken for histological study; no other procedure was attempted.

Fig. 2—Biopsy of jejunum taken at laparotomy (Feb. 24, 1956), showing œdema of the submucosa and perivascular cellularity (× 45).

Microscopic examination of the intestinal wall was reported to show " marked œdema of the submucous layer and infiltra-

tion by plasma cells, macrophages, and eosinophils (fig. 2). A more acute inflammation was present in the region of the inner circular muscle layer, with infiltration by polymorphs and a few eosinophils. The lymph node shows non-specific sinus catarrh ".

Three weeks after operation the patient was free from symptoms and was discharged. During her stay in hospital daily blood-counts showed continuing leucopenia; there was no evidence of L.E.-cell phenomena. Snapper's test on a 2-hour clot was likewise negative. The E.S.R. had remained around 100.

She remained well for only twelve days; then she had a typical attack and she was readmitted on April 3. The white count had fallen to 700, with 61% lymphocytes. On this occasion the attack subsided without drip and suction on 25 mg. promethazine q.i.d. and her stay in hospital was only eight days.

The fifth attack of intestinal obstruction came sixteen days later and was again severe enough to warrant admission. Drip and suction therapy was not required, and the episode subsided in three days on cortisone (200 mg. daily). She was discharged after twelve days.

A sixth attack a month later subsided at home on four days of intensive cortisone therapy (250 mg. daily); and yet another, a month after, on the same regime. Maintenance therapy with promethazine 25 mg. t.d.s. was now instituted. Leucopenia and a high sedimentation-rate continued unchanged. She had an eighth attack in September, 1956, while she was still taking the anti-histamine, and it also responded to cortisone. The anti-histamine was accordingly stopped and daily cortisone (50 mg.) and oral potassium supplements substituted.

On Oct. 15, 1956, she was readmitted. Three days before she had developed swelling of the joints of the fingers, wrists, and ankles and had become strange in her behaviour. She was found to be confused, irrational, and extremely restless to the point of manic excitement. The temperature was 100°F, pulse-rate 106. The liver was enlarged to a fingerbreadth below the costal margin, and there was spindle-shaped swelling of the interphalangeal joints of both hands. There were no organic neurological signs.

The maniacal state deteriorated and she was transferred to the Royal Edinburgh Hospital for Mental Disorders where she remained from October, 1956, to June, 1957. During this time she was kept under observation by one of us (W. S.) and no further gastro-intestinal episodes occurred. Abnormal loops of small intestine were still obvious in barium-meal studies, however, and leucopenia and high E.S.R. persisted. There were several episodes of swelling and pain in the joints of hands, arms, and legs. Rubbery, enlarged glands became palpable in the axillæ and groins. Peripheral blood and marrow remained free of L.E. cells and Snapper's test was still negative.

In June, 1957, the fingernails gradually became a dense white colour. Her mental state, which had fluctuated from maniacal excitement to mute withdrawal requiring forced feeding, had improved considerably, and on June 6 she was well enough to be transferred to the Gastro-intestinal Unit. Psychometric studies before transfer had demonstrated impairment of conceptual function, learning efficiency, comprehension, and both expressive behaviour and motor coordination. A lumbar puncture showed 35 cells per c.mm. and 61 mg. per 100 ml. of protein in the cerebrospinal fluid. In view of this it was believed that she now suffered from an organic disorder of the brain and the original concept of a steroid-induced disease was abandoned.

Liver-function tests were now abnormal: thymol turbidity 9 units, zinc turbidity 23 units, and cephalin-cholesterol flocculation 4+. Needle biopsy of the liver showed slight thickening of the portal tracts but no other more specific change. The bromsulphthalein retention test was normal. Biopsies of the enlarged glands in the groin showed only an increase in the lymphoid content and the fibrous stroma. A portion of muscle showed no evidence of arteritis in 140 sections.

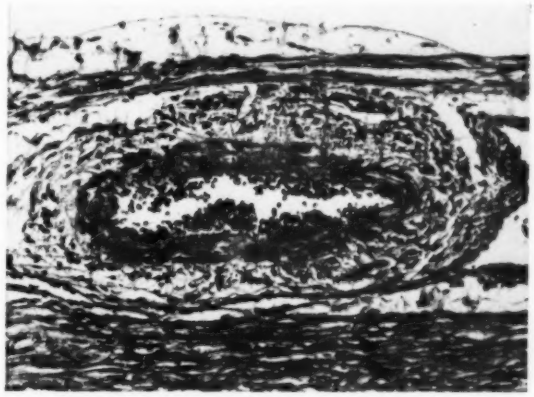

Fig. 3—Necropsy specimen. Vessel in serosa of stomach showing acute arteritis (×150).

She improved still further, gained weight, and was discharged on June 20, 1957. For four months she remained well and then a ninth attack of intestinal obstruction necessitated readmission, and drip and suction therapy. On Oct. 11 L.E. cells were present in large numbers in the peripheral blood. Snapper's test was now positive. Steroids (prednisolone 10 mg. per day maintenance) were resumed and she was allowed home. She returned to work in November, 1957, complaining only of moderate fatigue and amenorrhœa.

On Dec. 1957 there was a tenth attack of intestinal obstruction, which required admission and drip and suction therapy. Her knee-joints were inflamed. As the abdominal attack settled, there was gross deterioration in her cerebral state. L.E. cells were continually and abundantly present, and red cells as well as a large amount of albumin in the urine. Creatinine clearance was only 88 litres in twenty-four hours. Prednisolone dosage was increased but since catatonia and incontinence supervened she had to be transferred to the mental hospital. From January to March, 1958, there was rapid improvement, but on March 27 a severe recurrence (eleventh) of the acute abdominal disorder necessitated readmission to the Gastro-intestinal Unit.

Ptosis of the left eyelid and athetoid movement of the arms were noted. The intestinal obstruction was quickly relieved but over the next two weeks her general state deteriorated and she lapsed into coma. There was bleeding from the gums, and bilateral extensor plantar reflexes. She died in coma on April 30, 1958.

Postmortem Findings

Necropsy was performed four and three-quarter hours after death. The following is a summary of the pathological findings in the alimentary tract. A fuller account will be given elsewhere (Gordon 1959).

The œsophagus showed œdema involving the full thickness of the wall. The stomach was dilated and contained 2 litres of fluid. The small intestine from the duodenojejunal flexure onwards was dilated, the wall thick and œdematous, the mucosa slightly hyperæmic, and showing a few small ulcers. The large intestine was also œdematous with thickening of the wall most marked in the cæcum and lower part of the sigmoid colon. Moderately enlarged lymph-nodes were present in the neck, axillæ, groins, mediastinum, and along the abdominal aorta. All other viscera and tissues including the bone-marrow, the joints, and the brain appeared macroscopically normal.

Histological study revealed acute and chronic vascular lesions of disseminated lupus erythematosus throughout the length of the alimentary tract. Arterial lesions were present in an acute form in the œsophagus, stomach, and colon, and in a chronic form in the small intestine. They consisted of periadventitial cuffs of plump dark cells (presumably histiocytes or fibroblasts) arranged more or less radially in the early lesions

Fig. 4—Necropsy specimen. Vessels in serosa of jejunum showing concentric adventitial fibrosis of chronic type (× 150).

(fig. 3), and with a progressively more circumferential distribution until some late lesions showed the "onion-skin" fibres resembling those typically encountered in the spleen (fig. 4). In the acute lesions the smooth muscle of the media of the vessels occasionally showed degenerative changes, and sometimes this amounted to necrosis. More rarely thrombosis was present. Outwards from the adventitia the perivascular connective tissue was œdematous and sparsely infiltrated with mononuclear cells, together with an occasional eosinophil. The overlying epithelium of the alimentary tract was largely intact, but in the jejunum there were old superficial ulcers densely infiltrated with plasma cells. In the colon there was some necrosis of the smooth muscle, with neutrophil infiltration and arterial lesions of intermediate age (fig. 5). The immediate cause of death was acute infective peritonitis and a heavy growth of *Escherichia coli* was obtained from the peritoneal fluid.

A reappraisal of the original lymph-node and jejunal biopsy material was then made and previously undetected lesions similar to those revealed at necropsy could now be recognised. The lymph-node vessels showed adventitial fibrosis of the "onion-skin" type and in the jejunum the acute type of vascular lesion was present in association with the massive submucosal œdema. In fact, periadventitial cellularity was sufficiently marked in the acutely inflamed circular muscle coat to have suggested the correct diagnosis.

Fig. 5—Necropsy specimen. Section of wall of colon showing œdema, neutrophil infiltration, and necrosis of muscle (× 45).

Discussion

Disseminated lupus erythematosus in which abdominal pain, vomiting, and diarrhœa were features was recorded by Dubois (1953) and he drew attention to the hæmorrhages into, or infarction of, the bowel wall.

In the group of 105 cases of Harvey et al. (1954) 1 patient had bloody diarrhœa and abdominal pain, and necropsy showed extensive arteritis with thrombosis of the vessels and superficial ulceration of the mucosa in the small intestine. 4 other patients had abdominal pain and diarrhœa, but the arteritis and mucosal ulceration were localised to the large bowel.

In 5 of the 7 cases with gastrointestinal symptoms in the group of 87 cases reported by Brown et al. (1956) intestinal peristalsis was poor and tone in the bowel was reduced, with symptoms and signs of intestinal obstruction; but structural lesions were not noted. In 1 patient, dilatation of the second and third parts of the duodenum mimicked the superior mesenteric syndrome and a similar segmental ileus was present respectively in the stomach and in the ileum in another 2 patients. Abnormal necropsy findings in the alimentary tract were found in only 2 cases, 1 showing intestinal œdema and submucosal hæmorrhages in the small intestine, and the other depots of collagen in the submucosa of the stomach. 1 of their cases closely resembled ours, with episodes of acute small-bowel obstruction. At laparotomy the jejunum was distended, œdematous, and congested over a length of 30 cm. Unfortunately, histological studies were not made.

We suggest that lupus erythematosus of the bowel can be recognised both clinically and at operation in cases of intestinal obstruction. Recurrent attacks of transient acute intestinal obstruction with segmental ileus on radiological examination in young subjects, especially women, with diarrhœa accompanied by pyrexia and leucopenia, should suggest the diagnosis even in the absence of other recognisable phenomena of the systemic disease. At laparotomy swollen, soggy, deeply injected lengths of small intestine are characteristic. The only difficulty in diagnosis—the differentiation between recurrent Crohn's disease and jejunitis acuta—may be resolved by observing the transient nature of the attacks, with either spontaneous resolution or rapid improvement on steroids or anti-histamines within seventy-two hours.

The intestinal ileus probably reflects an acute inflammatory reaction in the bowel wall, with a direct effect upon both the muscle and myenteric nerve plexus. Obstruction is due to obliteration of the lumen by massive œdema of the intestinal wall.

We are indebted to Dr. A. Gordon, of the pathology department of the Western General Hospital, for the detailed study of the pathological changes.

REFERENCES

Brown, C. H., Shirey, E. K., Haserick, J. R. (1956) *Gastroenterology*, **31**, 649.
Dubois, E. L. (1953) *Ann. intern. Med.* **38**, 1265.
Gordon, A. (1959) In preparation.
Harvey, A. M., Shulman, L. E., Tumulty, P. A., Conley, C. L., Schoenrich, E. H. (1954) *Medicine, Baltimore*, **33**, 291.
Osler, H. (1895) *Amer. J. med. Sci.* **110**, 629.

THE PULSELESS SYNDROME

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CLINICAL case-reports that have been published under the heading of pulseless disease describe a syndrome rather than a disease entity. Obstruction of the large arteries arising from the arch of the aorta may be due to several causes, including syphilitic aortitis, healed dissecting aneurysm, trauma, atheroma, and congenital vascular anomalies (Ross and McKusick 1953). Even when these conditions are excluded, the reported cases of arteritis of medium-sized and larger vessels do not always correspond with those in young Japanese women described by Takayashu (1908).

By common usage, pulseless disease implies an absence of pulses in the arms and sometimes in the neck, together with evidence of an inflammatory reaction such as fever, increased erythrocyte-sedimentation rate (E.S.R.) and raised serum-globulin level, or else histological evidence of arteritis near the origin of large vessels. These features were present in the following three cases, which appeared nevertheless to be examples of three different diseases.

Case-records

Case 1.—A woman of 33 consulted Sir Thomas Lewis (Lewis and Stokes 1942) because of fainting attacks followed by severe headaches. During one of these attacks she lost the sight of her right eye, and she also complained of aching of the arms while scrubbing and of numbness and blueness of the fingers.

On examination at this time her arms and carotid arteries were pulseless and she had optic atrophy on the right side. The systolic blood-pressure in the arms was about 50 mm. Hg although the pressure in the legs was 220/130 mm. Hg. She had anastomotic vessels in the distribution found with coarctation of the aorta but with the blood-flow in the opposite direction. The Wassermann and Kahn reactions were repeatedly negative.

This patient died five years later following a cæsarean section.

Pathological Examination

Necropsy (L. E. G.) showed very advanced atheroma of the whole of the aorta from 2–3 cm. above the valves to about 3–4 cm. above the aortic bifurcation. The affected portion was thickened and heavily calcified and there was much intimal thickening. The main vessels coming off the aortic arch were occluded by atheromatous thickening and old thrombus, but the brachial vessels and the internal carotid arteries in the skull were patent and their walls not thickened. The branches of the abdominal aorta, the common iliac vessels, and the pulmonary vessels were all normal. Other findings were left ventricular hypertrophy, well-developed arteriosclerotic changes in the kidneys, and extensive cerebral softening. The cause of death was pulmonary œdema.

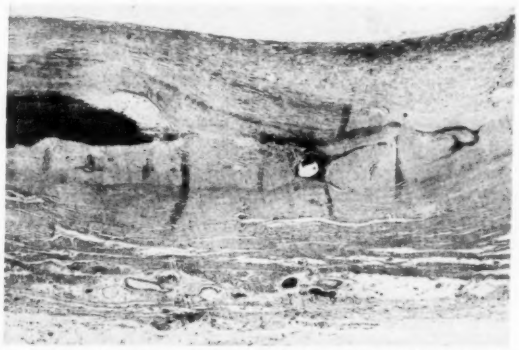

Fig. 1—Case 1: transverse section of the aorta showing extensive destruction of the media, much thickening of the intima, and fibrosis of the adventitiæ. (Weigert's elastic stain. ×11.)

Fig. 2—Case 1: part of a transverse section of the common carotid artery. The lumen is almost obliterated by an organised thrombus; the media shows many areas of destruction; and there is a striking degree of fibrosis of the adventitiæ. (Weigert's elastic stain. ×85.)

On histological examination there was destruction of the musculoelastic media of the large arteries, considerable dense adventitial fibrosis, and severe narrowing of the lumen as a result of intimal proliferation and thrombosis (figs. 1 and 2). This appeared to be a classical case of Takayashu's disease with histological findings closely resembling syphilitic aortitis.

Case 2.—A woman of 39 was admitted to Guy's Hospital under the care of Dr. W. N. Mann in December, 1956, on account of a left-sided paralysis that had developed overnight. She had had frequent visual blurring and also attacks of giddiness followed by occipital headaches. On examination the only abnormal finding was spastic left hemiparesis, and carotid-artery thrombosis was suspected. The paralysis cleared completely; but six months later she was readmitted with intermittent claudication of the right leg. She now had impalpable pulses in the arms, except for the left ulnar artery which could just be felt. There were no pulses in the legs below the femoral arteries. Plethysmographic studies of the peripheral blood-flow (Prof. W. J. H. Butterfield and Mrs. A. May) showed that the blood-flow after twenty minutes of vascular occlusion was considerably below normal, not only in the right foot, which was the side of the claudication, but also in the left foot (fig. 3). The blood-flow in the hands during this test was even more reduced and was only about a tenth of normal. The only other abnormalities on investigation were an E.S.R. of 28 mm. in the first hour (Westergren) and a serum-globulin level of 3·7 g. per 100 ml. The bleeding and clotting times and the blood-platelets were normal.

This patient's early progress has been reported elsewhere (Lessof 1958). In a few months ischæmic symptoms developed

in the arms, and these progressed despite prolonged anticoagulant and steroid therapy. Within fifteen months of her first symptom she died, and by this time she had gangrene of the left hand and foot and was having severe right-sided loin pain and hæmaturia.

Pathological Examination

Necropsy (Dr. G. K. Missen) showed thrombosis of most of the main arteries, including the left subclavian at its origin, the basilar, and the aorta up to half-way across the mouths of the renal arteries. The inferior vena cava was also thrombosed, but the carotid arteries were patent. In the brain there were many old cortical and subcortical infarcts including one in the right internal capsule and one below the right occipital pole near the visual cortex.

Histologically the arterial walls were remarkably normal. There was no destruction of the media, the adventitia was normal, and the only abnormality of the intima was occasional atheroma. The thrombi showed various degrees of organisation: this was most advanced in the basilar artery (fig. 4). Death was due to terminal pyelonephritis and to an unidentified thrombotic condition that was not associated with arteritis.

Case 3.—A young woman of 21 attended Guy's Hospital as a patient of Dr. Charles Baker complaining of retrosternal pain at times of excitement. When she was 13 she had had an attack of rheumatic fever which left her with severe aortic incompetence; both radial pulses were then present. Two years later, while at a residential school for children with heart-disease, she had repeated menorrhagia. After several blood-transfusions, radiophosphorus was inserted into the uterus and finally hysterectomy was performed. At the age of 20 she was seen by Dr. J. Litchfield, of Birmingham, who noted the absence of pulses in the arms. Subsequently bacterial endocarditis developed, and this responded to treatment with penicillin. Her symptoms included visual blurring in both eyes. When excited she had a blotchy erythema of the shoulders and face and severe anginal pain.

On examination she had some anastomotic vessels around the right optic disc. The signs of aortic incompetence were gross as far as the heart and carotid arteries were concerned, but, in contrast, no pulses were palpable in the subclavian vessels or in the arms. Peripheral blood-flow studies (Professor Butterfield and Mrs. May) showed a grossly diminished blood-flow in the hands and also a diminished blood-flow in the left foot although there were no symptoms associated with this. Electrocardiography showed evidence of left ventricular hypertrophy and there was inconstant inversion of the T waves

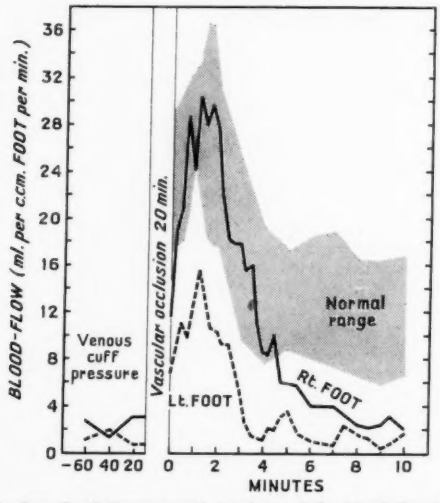

Fig. 3—Case 2: plethysmograph tracings of the blood-flow in the feet after vascular occlusion for 20 minutes. There is moderate reduction of flow in the right foot and much reduction in the left.

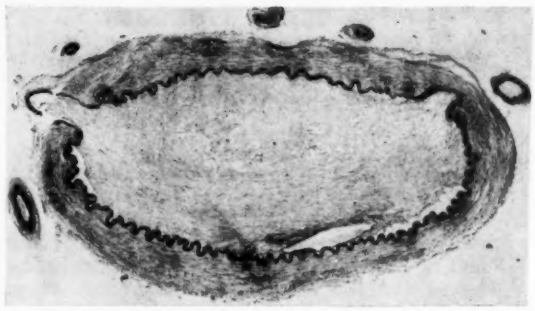

Fig. 4—Case 2: transverse section of the basilar artery showing an extensively organised thrombus but apparently normal wall. (Weigert's elastic stain. ×60.)

in leads V_{5-6}. The blood-count was normal, but there were numerous L.E. cells. The E.S.R. was 41 mm. in the first hour (Westergren); the serum-albumin level was 3·1 g. per 100 ml. and the serum-globulin 3·8 g. per 100 ml. There was a falsely positive Wassermann reaction and a negative treponema immobilisation test. An antinuclear factor was demonstrated in the serum by the method of Holborow et al. (1957).

Systemic lupus erythematosus was diagnosed, and for the past ten months this patient has been receiving steroid therapy. Her E.S.R. has returned to normal, but the symptoms and signs associated with her cardiovascular disease have shown little or no change and in the past month acute generalised polyarthritis has developed.

Discussion

The characteristic feature of the disease described by Takayashu is obliterating arteritis of large vessels. The loss of pulse is due chiefly to the severe narrowing of the lumen that results from intimal proliferation. Thrombosis apparently plays a less important part, although thrombi do occur. Atherosclerosis is secondary to the arteritis, and Ask-Upmark and Fajers (1956) have shown that atherosclerosis does not occur distal to the obstruction. Our case 1 (originally reported by Lewis and Stokes) had all the features of this disease, and the brachiocephalic branches of the aorta showed considerable intimal proliferation as well as destruction of the media, both muscle and elastic fibres, and adventitial fibrosis. The histological similarity of the aortic lesions to those seen in syphilis and those recently reported in some cases of ankylosing spondylitis (Ansell et al. 1958) was remarkable. No other evidence of either of these diseases, however, was found either clinically or at necropsy. The high blood-pressure detected in the legs during life was associated with renal disease, and a similar finding has been reported by Ask-Upmark (1954).

Case 2, although superficially similar, was clearly an example of another condition. Intermittent claudication may be associated with the obliterating arteritis of Takayashu, but peripheral gangrene is not a known feature of this disease. Thrombosis of arteries without arteriosclerosis or arteritis is rare, but this has been described in thrombophilia (Nygaard and Brown 1937). Our patient's condition differed from thrombophilia in the size of the arteries involved as well as in the blood-picture. Allen et al. (1955) have suggested the name "thrombosing disease" for cases of sudden arterial thrombosis without known cause, and this name seems to describe the present case aptly.

Case 3 differed from both previous cases. Investigations into the cause of the positive Wassermann reaction

revealed that the patient had serological evidence of systemic lupus erythematosus despite the absence of most of the clinical features of this condition. In the presence of normal carotid arteries and of aortic incompetence, the patient's condition was not entirely typical of Takayashu's disease; but this is not the first case reported of pulseless disease with aortic incompetence (Jervell 1954).

Our patient clearly has disseminated lupus erythematosus, but the absence of the pulses in the neck and arms cannot be attributed definitely to this condition. Although vascular lesions are common in disseminated lupus the affected vessels are usually small and peripheral, resulting in the characteristic nail-fold and pulp lesions. Larger vessels are occasionally affected (Keat and Shore 1958) resulting in extensive gangrene of either legs or arms; but no case of disseminated lupus erythematosus has, to our knowledge, been observed with lesions affecting the main arteries at their origin from the aortic arch. The patient is known to have had rheumatic fever as a child, and rheumatic aortitis with involvement of the first part of the aorta has been recognised since von Glahn and Pappenheimer's (1926) classical description, although thrombotic obstruction has not been described as a consequence of such a lesion. The alternative—namely, that her "pulseless" state is independent both of her disseminated lupus and her rheumatic heart disorder—appears to us highly improbable. In any event this case exemplifies yet another ætiological variant of a clinical syndrome which has several causes.

Summary

Three cases are described in which there was a loss of pulses in both arms in women.

The lesions were the obliterating brachiocephalic arteritis of Takayashu in one, an unidentified thrombotic condition of the large arteries in the second, and arterial occlusion associated with systemic lupus erythematosus in the third.

Blood-flow studies in the limbs helped to define the extent of peripheral arterial involvement, even when symptoms were absent.

We wish to thank Dr. C. G. Baker and Dr. W. N. Mann, who allowed us to study their patients and at whose suggestion this study was made; and Prof. W. J. H. Butterfield, Mrs. A. May, Dr. T. M. Chalmers, Dr. G. K. Missen, and Dr. J. Litchfield for their help.

REFERENCES

Allen, E. V., Barker, N. W., Hines, E. A. (1955) Peripheral Vascular Disease. Philadelphia.
Ansell, B. M., Bywaters, E. G. L., Doniach, I. (1958) *Brit. Heart J.* **20**, 507.
Ask-Upmark, E. (1954) *Acta med. scand.* **149**, 161.
— Fajers, C. J. (1956) *ibid.* **155**, 275.
Holborow, E. J., Weir, D. M., Johnson, G. D. (1957) *Brit. med. J.* ii, 732.
Jervell, A. (1954) *Amer. Heart J.* **47**, 780.
Keat, E. C. B., Shore, J. H. (1958) *Brit. med. J.* i, 25.
Lessof, M. (1958) *Guy's Hosp. Rep.* **107**, 53.
Lewis, T., Stokes, J. (1942) *Brit. Heart J.* **4**, 57.
Nygaard, K. K., Brown, G. E. (1937) *Arch. intern. Med.* **59**, 82.
Ross, R. S., McKusick, V. A. (1953) *ibid.* **92**, 701.
Takayashu, M. (1908) *Acta Soc. ophthal. Jap.* **12**, 554.
von Glahn, W. C., Pappenheimer, A. M. (1926) *Amer. J. Path.* **2**, 235.

"... Addiction to the bottle of medicine, or 'my tablets,' or whatever treatment has been prescribed, is now so common that one must stress the great importance of *stopping* the treatment as soon as it is reasonable to do so. This is a formidable task, because the symptom service which has been developed since the inception of National Health Insurance in 1911 ... is essentially a script-writing service which is neither healthy nor sane. ... The general practitioner ... is facing a decision which can be framed like this: 'Am I aiming to be a good doctor, or am I simply the manufacturers' agent and the purveyor of placebos?'"—Dr. SINCLAIR WILSON, *J. med. Educ.* 1958, **33**, 797.

SPHYGMOMANOMETER FOR THE NEWBORN

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IN man the arterial blood-pressure appears to have been less frequently measured in the first few days after birth than at any other period of life, and such measurements are not included in the routine clinical assessment of newborn babies. This is the more surprising because it is during the neonatal period that the circulatory system undergoes the greatest changes in its physiology, and the greatest risks of stress due to blood-loss, hæmolysis, trauma, or inadequate pulmonary ventilation. Also, the early diagnosis of certain congenital malformations depends on accurate measurements of the blood-pressure. The reason for this lack of information would appear to be the lack of any method of measuring the blood-pressure at this age which is sufficiently convenient, accurate, and generally accepted.

The two main technical difficulties about using a standard sphygmomanometer for the newborn are: (*a*) to find a sufficiently sensitive indicator of the arterial pulsation beyond the occluding cuff which is at the same time simple, portable, and suitable for everyday clinical use; (*b*) to decide the correct width of the occluding cuff itself, for babies of different sizes, and to make a cuff which is simple to apply and easy to clean between cases.

We describe here an instrument that we have developed during the past year and which we believe goes a long way towards solving these problems, at least in so far as the systolic pressure is concerned.

The Pulse-indicator

Previous Observations

The two simplest methods of detecting the arterial pulsation beyond the sphygmomanometer cuff are palpation and auscultation. In the newborn, auscultation was used by Salmi (1936) and by Browne and Dodds (1936). Palpation appears to have been more commonly used—notably in the classic studies of Woodbury et al. (1938). But the evidence from these and other reports suggests that neither of these methods could be regarded as entirely satisfactory in small babies. Seitz and Becker (1920) were unable to feel the radial pulse with sufficient confidence to make any observations in the majority of the babies whom they examined within the first 3 days of life. Brash (1949) often had difficulty in feeling the radial pulse, but only in four cases was the attempt abandoned. Holland and Young (1956) decided that it was more reliable to palpate the brachial artery; but they needed to record "the average of two or three readings" for each of their observations, and did not state the range of variation between successive readings.

Of those who discarded these two methods, the majority preferred to use oscillometry. Rucker and Connell (1924), for instance, had found that "auscultation was uncertain and often impossible in very small infants", and that palpation was "impossible as a rule". But there are inherent defects in oscillometry, and it was discarded as unsatisfactory by Robinow et al. (1939). Goldring and Wohltman (1952) began to use the

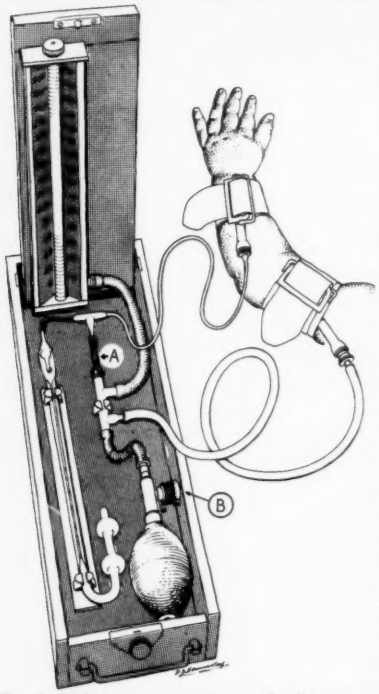

Fig. 1—Sphygmomanometer ready for use (the small pair of artery forceps for clamping the tubing at A is not shown).

The two connecting pieces within the box are made of glass. The shaded lengths of flexible tubing within the box are made of rubber: the unshaded lengths running to the cuffs are of portex tubing (no. 4 for the forearm and no. 8 for the upper-arm cuff).

relatively crude flush method because they found that they could not use either auscultation or palpation with sufficient confidence in small babies. Much more sensitive pulse-indicators were described by Keuth (1955), who used a microphone connected to an electrocardiograph, and by Schaffer (1955), who used an impedance plethysmograph. Schaffer, who compared his instrument carefully with simpler methods, found that by auscultation he could not obtain a satisfactory reading at all in a quarter of the newborn babies whom he examined, and noted that "neither palpation nor the flush method appears to be suitable as a clinical method", since both were "erratic and unreliable". Unfortunately, both the very sensitive pulse-indicators which these workers described involve the use of apparatus which is too complex and cumbersome for ordinary clinical use.

The Present Instrument

The pulse-indicator which we are using appears to be sufficiently sensitive, yet it is very simple both to make and to use, and it fits into the box of a standard sphygmomanometer. It consists of an inflatable cuff around the baby's forearm, connected by flexible tubing to a straight glass capillary tube whose lumen contains an interrupted column of xylol, beyond which is a "cushion" of compressible air against which the xylol can be moved by pressure changes within the forearm cuff. Small changes in the volume or the tension of the tissues of the baby's forearm underlying the cuff, such as those produced by the pulsation of the arteries, cause easily visible movements of the "beads" of xylol in the lumen of the capillary glass tube. The underlying principle of this instrument was suggested to us by R. V. Platou (personal communication); and we have recently found that a similar principle, but using a different visual system which is cumbersome and suitable only for cooperative patients, was described by Evans and Mendelssohn (1946).

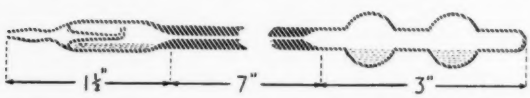

Fig. 2—Detailed structure of glass portion of pulse-indicator.

The 7-inch length of capillary tubing has a bore of 1 mm. The 3-inch length of thin-wall tubing containing the distal xylol reservoir is bent through an angle of 180° in the horizontal plane, as shown in fig. 1. The volume of the "cushion" of air contained in this portion, with its two bulbs, is approximately 8 ml.

The general layout of our instrument, in use, is shown in fig. 1, and the detailed structure of the glass portion of the pulse-indicator in fig. 2. The procedure for taking a reading is as follows:

1. Inflate the whole system to about 60 mm. Hg, making sure that one or more "beads" of xylol enter the lumen of the glass capillary tube. This can be ensured, if necessary, by tilting the instrument during inflation, to bring some xylol into the lumen from either the proximal or the distal reservoir.

2. Isolate the pulse-indicator from the rest of the system by clamping the rubber tubing at A with a small pair of artery forceps. If it is free of leaks, the pulse-indicator system should thenceforward remain at a constant pressure until the clamp is released.

3. Allow the pressure in the rest of the system, including the cuff on the upper arm, to fall to zero by opening the control valve at B. The xylol "beads" in the glass capillary tube should immediately show a characteristic rhythmical and constant to-and-fro movement, representing the pulsation of the arteries of the forearm. When the instrument is working satisfactorily the "beads" move about 2–3 mm. with each pulsation. If the excursion is less than this, the pressure should be released and the cuff reinflated to a different pressure until the optimal level is found. This is usually at about the level of the baby's systolic pressure. Active movements of the baby's forearm produce extensive and irregular movements of the beads, which do not resemble those caused by the arterial pulsation, but do tend to obscure them. If the baby is too restless, therefore, one must wait until he settles down sufficiently for a satisfactory reading to be obtained.

4. Count the baby's pulse-rate, as shown by the pulse-indicator.

5. To record the systolic pressure, inflate the cuff round the upper arm until the xylol "beads" cease to move, and then let the pressure fall very slowly until the characteristic movement reappears. At first one sees only an occasional beat; then short runs of beats, as a rule, due to small variations in systolic pressure with different phases of respiration; then all the beats come through, as shown by their regularity, and if necessary by comparing their rate with that recorded in stage 4. We record the systolic pressure as the level of the mercury when all the beats first come through. Its correctness can be confirmed by reinflating the bag to raise the mercury 3–4 mm. and allowing it to fall slowly through the critical range again. The forearm cuff can be left inflated for at least a quarter of an hour without causing any apparent harm, and readings can be taken several times each minute if desired, and if the baby remains quiet.

6. The diastolic pressure may be represented by the mercury level at which the excursion of the xylol "beads" regains its maximum range. But we have found this end-point relatively difficult to judge by eye, and have not attempted to record it routinely. It has been suggested to us that an instrument which records the changes in the Korotkoff sounds is probably more suitable for accurately measuring the diastolic pressure.

Comparison with Auscultation and Palpation

We have compared this pulse-indicator with auscultation and palpation, both for ease and for accuracy. In a series of tests two observers worked together—one trying

to detect the first return of the arterial pulsation beyond the occluding cuff by auscultation, palpation, or vision, the other controlling the pressure and reading off the level of the mercury representing the systolic pressure when asked to do so by his colleague. Also, to eliminate the effect of bias on our part, we enlisted the help of some of our students in these tests. In each baby whom we tested we tried to make a series of five " blind " readings by each of the three methods in rapid succession, so that we could compare the range of variation and the absolute level of the readings obtained by each of them.

We found that in certain babies we could not feel or hear the pulse with sufficient confidence to take any readings at all by one or both of the older methods; and in others the observer, after making a satisfactory start, tired so rapidly when using one or other of these two methods that he was unable to take the full set of readings. Such babies, in fact, formed the majority of those whom we tried to include in the test. But in no case was it found impossible, or prohibitively tiring, to make five readings in succession by the xylol pulse-indicator—though there was occasional delay owing to restlessness on the baby's part. In other words, we found the xylol pulse-indicator incomparably easier and less tiring to use than the older methods; and neither the noise nor the other conditions commonly encountered in clinic practice diminish its accuracy.

We were able to make a full comparison of the accuracy of the three methods in only four babies, two of whom we examined twice. The results are summarised in table I.

TABLE I—RESULTS OF FIVE " BLIND " READINGS BY EACH OF THE THREE METHODS IN SUCCESSION (results expressed in mm. Hg)

Baby	Palpation		Auscultation		Vision	
	Range	Median	Range	Median	Range	Median
A	12	56	8	60	4	74
B	22	80	14	68	4	68
C1	12	46	8	58	2	58
C2	6	54	24	56	2	58
D1	12	46	4	36	2	54
D2	16	40	22	46	6	54
Average	13		13·3		3·3	

Babies C and D were each tested by two different pairs of observers.

If the range of variation within a series of readings taken by a single pair of observers, and the difference between the results obtained by different pairs of observers in the same baby, are inversely related to the accuracy of the method, then the xylol pulse-indicator was much the most accurate of the three methods tested—even in these few babies who were selected as the most favourable for the older methods by the fact that the full series of readings could be carried out at all. These results generally agree with those of Schaffer (1955).

We have found that, using the xylol pulse-indicator, a trained observer can reliably keep within a range of error of 4 mm. Hg, at most, so that a single reading can be accepted as valid for all practical purposes; which is a great advantage when one is aiming to detect changes in blood-pressure by taking a series of readings in rapid succession.

A preliminary account of some of the observations made with this apparatus appears elsewhere (Ashworth and Neligan 1959).

The Occluding Cuff

Width

In older subjects, increasing the width of the occluding cuff beyond the optimum width produces little or no depression of the readings below the correct level. The situation is different in the newborn, however. The careful work of Woodbury et al. (1938) and Robinow et al. (1939) showed that if too wide a cuff is used the readings by the indirect method are depressed below those simultaneously recorded by the direct method through a needle inserted into an artery. They found that agreement between the two methods was closest when they used a cuff 2·5 cm. (1 in.) wide, relying on palpation of the radial artery as the pulse-indicator. Our results (table I) and those of Schaffer (1955) suggested that when a more sensitive pulse-indicator was used the readings obtained with such a cuff might tend to be too high. We were not in a position to check our results by the direct method, so decided to carry out a simple clinical investigation of the effect of using a wider cuff.

TABLE II—DIFFERENCES BETWEEN READINGS TAKEN IN SUCCESSION WITH 1 IN. AND 1½ IN. CUFF IN BABIES OF DIFFERENT WEIGHT-GROUPS

Weight (lb.)	No. of babies	Range of differences	Mean of differences
5–6	5	0–14	6·5
6½–7½	9	4–14	7·5
8–9½	10	0–14	6·2
Over 10	5	4–14	9·0

The most important variable factors determining the correct width for the cuff are the circumference and the length of the baby's upper arm (Robinow et al. 1939). Neither of these is easy to measure accurately; but they should bear some sort of relation to the baby's weight, which is routinely recorded, and so we compared the readings taken with a 1 in. (2·5 cm.) and with a 1½ in. (3·75 cm.) cuff in babies of different weight-groups. In all cases the reading obtained with the wider cuff was the same as, or lower than, that obtained with the narrower one; in four it was as much as 14 mm. Hg lower; but neither the range nor the mean of the differences showed any systematic tendency to be greater in the heavier babies (table II).

These findings suggest that the baby's weight does not affect the chance that a reading with a wider cuff will be lower than one taken with a narrower cuff. Since uniformity of practice is clearly desirable, we decided to use a cuff 1 in. (2·5 cm.) wide for all our observations. This is the widest cuff that can be snugly fitted round the upper arm of even the smallest babies. It is also suitable for the forearm cuff of the pulse-indicator, in our apparatus, and it is convenient to have only one size of cuff in routine use.

Structure

The length of the inflatable bag is determined by the fact that it must completely encircle the limb. For the upper arm of the newborn we have found a bag 6 in. (15 cm.) long quite adequate; but in some of the larger babies a rather longer bag may be required to surround the thigh.

The choice of material for making the cuffs was determined by the need for them to fit snugly, to be easily applied, and to be easily cleaned, bearing in mind that the baby's arm might be covered with vernix, blood, or meconium at the time when the first readings had to be taken. We have found polyvynylchloride (P.V.C.) sheeting very suitable; and it has the additional advantages of being cheap, and easy to make up in any workshop where there is a high-frequency welder to which electrodes of suitable shape can be fitted. The thickness of the sheeting used for the inflatable bag is 0·01 in., and for the strap 0·02 in. The P.V.C. tubing welded into the bag is 'Portex' no. 10H. This is the only point at which the welding may fail to stand up to the pressures to which it is subjected in use. Earlier failures due to this cause have been virtually eliminated by preparing the portex tubing before welding it into the sheet-

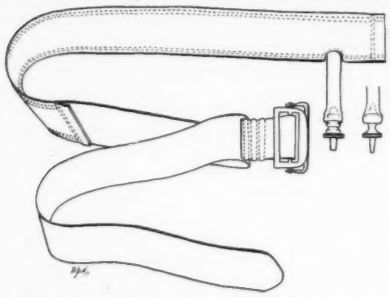

Fig. 3—Cuff made of welded P.V.C. sheeting.
The portex tubing is no. 10H. The internal measurements of the bag are 1 in. × 6 in. The strap is 11 in. long, and the buckle is attached 4 in. away from the bag. The whole can be cleaned with a 1: 500 solution of cetrimide.

ing. This is done by slipping the end of the tubing over a heated glass cone of suitable shape and size. The softened end of the tubing is thus expanded slightly so that it is more easily everted and firmly united with the sheeting by the circular electrode during the subsequent welding process. This is the first step in making the bag (see fig. 3).

The connector for joining the occluded cuff to the no. 8 portex tubing leading to the apparatus is the male portion of the standard sphygmomanometer connection. The connector for the forearm cuff, to fit no. 4 portex tubing, is the standard olive-ended Record-fitting adaptor used in blood-transfusion sets. The buckle illustrated is very easy to apply, and grips the strap firmly without in any way damaging it.

Summary

A sphygmomanometer has been designed to overcome the inherent difficulty and inaccuracy of the older methods of auscultation and palpation when used for measuring the blood-pressure in the newborn, and at the same time to avoid the complexity and bulk of the more sensitive pulse-indicators.

The method is visual. From a cuff inflated around the forearm the arterial pulsation is transmitted to an interrupted column of xylol in a glass capillary tube, giving rise to a characteristic movement of the xylol " beads ". Systolic pressures can be recorded with ease, and at intervals of a few seconds if desired, the range of error being at most 4 mm. Hg. Diastolic pressures cannot be recorded accurately with this instrument. The pulse-indicator fits into the box of a standard sphygmomanometer.

The width of the occluding cuff used is 1 in. (2·5 cm.). This is an arbitrary choice, based largely on convenience, since no direct measurements of the arterial pressure have been made for comparison with the readings by the indirect method.

The cuffs are made of polyvinyl-chloride sheeting, which is cheap, easy to make up, and easy to clean after use.

We are most grateful to Prof. E. A. Pask for much helpful advice about the development of this instrument; and to Mr. D. Hammersley, of the Department of Surgery, for the drawings.

REFERENCES

Ashworth, A. M., Neligan, G. A. (1959) *Lancet*, i, 804.
Brash, A. A. (1949) *Arch. Dis. Childh.* **24**, 107.
Browne, F. J., Dodds, G. H. (1936) *Lancet*, i, 1059.
Evans, D. S., Mendelssohn, K. (1946) *Brit. med. Bull.* **4**, 99.
Goldring, D., Wohltmann, H. (1952) *J. Pediat.* **40**, 285.
Holland, W. W., Young, M. (1956) *Brit. med. J.* ii, 1331.
Keuth, V. (1955) *Z. Kinderheilk.* **77**, 443.
Robinow, M., Hamilton, W. F., Woodbury, R. A., Volpitto, P. P. (1939) *Amer. J. Dis. Child*, **58**, 102.
Rucker, M. P., Connell, J. W. (1924) *ibid.* **27**, 6.
Salmi, T. (1936) *Acta pædiat., Stockh.* **18**, 92.
Schaffer, A. I. (1955) *Amer. J. Dis. Child.* **89**, 204.
Seitz, A., Becker, F. (1920) *Zbl. Gynäk.* **44**, 1338.
Woodbury, R. A., Robinow, M., Hamilton, W. F. (1938) *Amer. J. Physiol.* **122**, 472.

CHANGES IN THE SYSTOLIC BLOOD-PRESSURE OF NORMAL BABIES DURING THE FIRST TWENTY-FOUR HOURS OF LIFE

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WE show here that in normal babies the systolic blood-pressure falls during the first few hours after delivery, sometimes to little more than half the initial level. We also report a preliminary study of the effects of interrupting the umbilical circulation on the systolic blood-pressure of normal babies.

Material and Methods

Of the 80 babies whom we have studied, 20 can be regarded as normal in every respect. A controlled vertex delivery followed an uncomplicated pregnancy and labour, with no evidence of fœtal distress; the baby's clinical condition at birth was good, with immediate onset of normal respirations, and good tone and colour. The birth-weight in every case was over 6 lb. (2750 g.), with a mean of 7 lb. 10 oz. (3450 g.). In 8 cases the umbilical cord either had to be clamped and cut during the delivery because it was found to be round the baby's neck, or was clamped immediately the delivery had been completed. In the remaining 12 cases the cord was left to pulsate, with the baby lying on the delivery table at a lower level than the uterus, until one or more readings of the systolic pressure had been obtained. In 9 of these cases the cord was then clamped as soon as pulsation could no longer be felt, between $1^1/_2$ and 6 minutes after delivery; in the remaining 3 it was clamped when still pulsating strongly, at intervals of $3^1/_2$, $5^1/_1$, and 20 minutes after delivery.

All observations were made with the sphygmomanometer described elsewhere (Ashworth et al. 1959), using the xylol pulse-indicator and an occluding cuff 1 in. (2·5 cm.) wide. This enabled us to record the systolic pressure and pulse-rate accurately and frequently, with the occasional limitation that the taking of an individual reading might be delayed by active movements of the baby's arm. The first reading was taken 1–5 minutes after the delivery had been completed; subsequent readings were taken every few minutes, or more frequently, during the first half-hour, and then at longer intervals during the remainder of the first 24 hours of life.

Changes in the First 24 Hours

In all 20 babies we observed a significant fall in the systolic pressure during the first 24 hours of life—far greater than the range of error of the instrument (which is at most 4 mm. Hg). The fall recorded in individual cases ranged between 14 and 54 mm. Hg; in 12 it was more than 30 mm. Hg, and the mean fall for all cases was 32 mm. Hg. The highest reading was recorded within the first 15 minutes after delivery in every case, except that of the baby whose cord was not clamped for 20 minutes, in whom there was a secondary rise soon afterwards, to just above the previous peak. The highest reading for the individual cases ranged between 62 and 116 mm. Hg (mean 92 mm. Hg). The lowest reading was recorded within 4 hours after delivery in the 8 cases whose cords were clamped early, and at some later stage (but always within the first 24 hours) in the 12 whose cords were

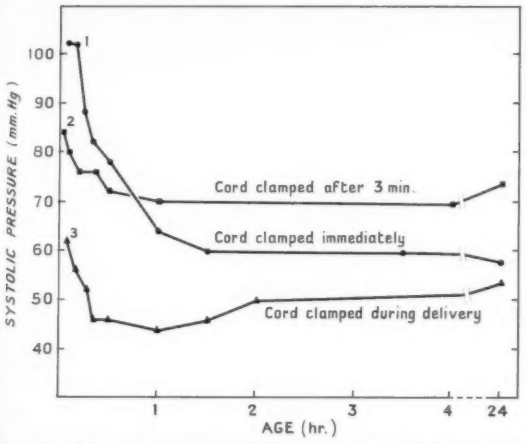

Fig. 1—Three representative records of the changes in the systolic pressure of normal babies during the first 24 hours of life.

clamped later. The lowest reading for the individual cases ranged between 44 and 76 mm. Hg (mean 60 mm. Hg). The curves of the changes recorded in 3 representative cases are shown in fig. 1.

The more or less steady rise in the systolic pressure day by day during the rest of the 1st week of life, about which there is general agreement in previous reports, has been confirmed in all our cases except 1, whose systolic pressure on the 7th day was still approximately the same as the lowest level recorded within the first 24 hours. In the remainder it had risen by 17–28 mm. Hg, but in none had it reached the highest level recorded during the first 15 minutes after delivery.

We also made some observations on changes in the body-temperature and pulse-rate of these same babies. The normal fall in body-temperature after birth roughly coincides with the period during which the systolic pressure falls. But we made sufficient simultaneous serial records of the rectal temperature and systolic pressure to be sure that there is no constant relationship between them. Commonly the rectal temperature began to rise again before there was any rise in the systolic pressure; occasionally the rise in systolic pressure preceded the rise in rectal temperature by a considerable interval. And in 2 cases where we took steps to minimise the fall in rectal temperature, the systolic pressure fell as in the other cases.

Changes in pulse-rate during the first 24 hours also seem to bear no constant relationship to the changes in systolic pressure. For instance, although the pressure changes recorded in case 1 (fig. 1) and case A (fig. 2) were similar, the changes in their pulse-rates were quite different.

In case 1 the pulse-rate at 4 minutes was 160 per minute; by $3^1/_2$ hours it had gradually fallen to 120, and by 22 hours it was up again to 152. In case A the pulse-rate when first recorded, at 2 minutes, was 96 per minute, just before the cord was clamped; by 5 minutes it was up to 140, and by 12 minutes back to 120—at which level it remained for the rest of the first 24 hours, except for a single drop at 23 hours to 104.

In other cases the pulse-rate varied remarkably little throughout the first 24 hours, irrespective of the changes in systolic pressure. In the majority of our cases the pulse-rate reached its lowest level at about the age of 48 hours, and then began to rise again; but in several it remained in the range 100–110 per minute throughout the first week of life.

Effects of Clamping the Cord

In the babies whose cords were clamped during or immediately after delivery, the systolic pressure reached its lowest level within 4 hours. Delay in clamping the cord, with the baby lying at a lower level than the uterus, delayed this fall, as has been mentioned. This delay was presumably due to the transfer of blood from the placenta to the baby's circulation while the cord continued to pulsate. Unfortunately the two groups of cases are not suitable for detailed analysis of this effect during its early stages, because they are not comparable in respect of the number of readings taken. In those where clamping was delayed we made every effort to obtain frequent readings, and regularly obtained ten or more in the first 15 minutes after delivery; but in those where clamping was immediate we usually obtained no more than three or four readings within the same period. It is noteworthy, however, that in no case where clamping was immediate did we record a rise of pressure above the initial reading; whereas in 3 of the 12 cases where clamping was delayed the pressure rose between 6 and 10 mm. Hg before the cord was clamped, and in a total of 7 cases it rose to 4–20 mm. Hg above the initial level after the cord was clamped.

Although delay in clamping the cord affected the time at which the systolic pressure reached its lowest level, it had no effect upon the actual level to which the pressure fell. For the cases with immediate clamping the mean of the lowest readings was 61 mm. Hg, and for those with delayed clamping it was 58. The means of the initial readings in the two groups were comparable, at 88·5 and 89 mm. Hg respectively.

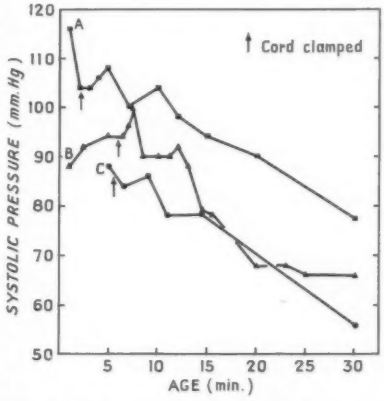

Fig. 2—Three representative records of the changes in the systolic pressure of normal babies during the first 30 minutes of life, to illustrate the effects of clamping the cord. The lowest recorded systolic pressures were: A, 64 mm. Hg at $6^1/_2$ hours; B, 58 mm. Hg at $2^1/_2$ hours; C, 52 mm. Hg at 24 hours.

Any direct and immediate effect on the systolic pressure which might result from interrupting the umbilical circulation would have to be sought in the records of the 3 cases whose cords were clamped while still pulsating well, at an interval after delivery during which one or more recordings had been obtained. In 1 of these cases the next reading, obtained 2 minutes after the cord was clamped, was 6 mm. Hg above the preceding one; in the other 2, readings obtained after $^1/_4$ and 1 minute respectively were exactly the same as the previous reading.

The less immediate effects should be detectable in the

records of all the cases where clamping was delayed, irrespective of whether the cord was still pulsating at the time. That there was a significant rise above the initial level in 7 of these 12 cases has already been mentioned. The highest level recorded was reached $2^1/_2$–13 minutes (mean 5 minutes) after the cord was clamped; the magnitude of the rise above the level recorded immediately before the cord was clamped ranged between 4 and 12 mm. Hg (mean 7). Since the pressure had already risen significantly above the initial level by the time the cord was clamped in 3 of these cases, it is important to be sure that the further rise was not simply a continuation of the effect of the so-called " placental transfusion " (see case B in fig. 2). The rise after clamping of the cord in case A (fig. 2) cannot be explained in this way, since the pressure had been falling steeply immediately beforehand. And the record of the case in which clamping was delayed for 20 minutes also suggests that there is a causal connection between the two events. From an initial reading of 94 mm. Hg the pressure rose to 110 at 11 minutes, when the cord was pulsating very strongly, then fell again to 102 immediately before the cord was clamped, while still pulsating strongly, and $2^1/_2$ minutes later was up to 112 mm. Hg.

The three curves in fig. 2 illustrate various responses to the clamping of the cord; and it is apparent that even in case C, where no significant rise in the systolic pressure was recorded, there is a strong suggestion that its fall was delayed for several minutes. Also, it seems possible that in this case a transient rise could have been missed because readings were not taken sufficiently frequently.

Discussion

Previous investigations of the blood-pressure of babies during the first 24 hours of life can be divided into two groups.

A direct method was used by Haselhorst (1929) and by Woodbury et al. (1938), who took readings of the pressure in the umbilical artery at birth, or in some cases even before delivery by cæsarean section. This method had two great advantages: it was accurate, and it enabled continuous tracings to be obtained. But it suffered from the limitation that readings could be continued only for a matter of minutes after delivery, until the circulation through the cord ceased. It is interesting to find that the range of initial readings quoted by Haselhorst—68–110 mm. Hg—almost exactly corresponds to our findings (62–116 mm. Hg).

Indirect methods of various kinds have been used more commonly, but no attempt seems to have been made to obtain readings immediately after birth (except by Woodbury et al. [1938], for comparison with their direct readings); and observations have not been continued throughout the first 24 hours. Holland and Young (1956) accepted a single set of recordings taken " within an hour of birth and often much sooner " as the systolic pressure " at birth ". Schaffer (1955) took very frequent readings at short intervals during the first day of life, but only during a single session lasting 30–90 minutes for each baby. Other reports simply refer to the pressure " on the first day of life ". These facts appear to explain why previous investigators have failed to detect the fall in systolic pressure, sometimes to little more than half the initial level, which we have found in all the normal babies whom we have studied.

Though it may be misleading to compare observations made in the young of different mammalian species at full term (Barcroft 1946), it is tempting to compare our findings with those reported by Dawes and his colleagues in newborn lambs, in which they have shown, by a series of precise experiments, the causes of many of the post-natal changes in the cardiovascular system which they have observed. Born et al. (1956) stated that " the pulmonary and systemic blood pressures normally fall when a mature fœtal lamb is well ventilated [artificially], because of the increase in pulmonary vascular conductance ". There is a strong suggestion, from their work, that the fall in systemic blood-pressure is an indirect indication of satisfactory opening-up of the pulmonary vascular bed, secondary to satisfactory expansion of the lungs. But we have seen no detailed study of the changes in the blood-pressure over the first 24 hours of life in healthy lambs which breathed spontaneously, compared with lambs whose lungs have been prevented from expanding fully by some mechanical means. Nor have we ourselves as yet had the opportunity to study the changes in a baby which had severe and prolonged difficulty in achieving initial expansion of the lungs.

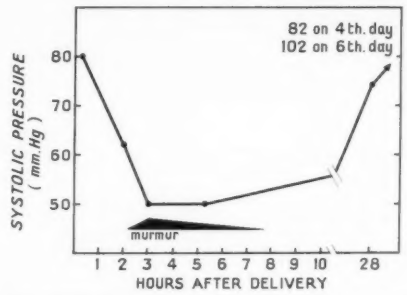

Fig. 3—The record of a baby who was delivered by forceps and took 6 minutes to establish normal respirations, to illustrate the relationship between the changes in systolic pressure and the development of a murmur which was thought to arise from the ductus arteriosus.

Changes in the calibre of the ductus arteriosus also might affect the systemic blood-pressure. For instance, sudden occlusion of the ductus in the newborn lamb usually causes a sharp rise in the systemic arterial pressure, as illustrated in table I and fig. 6 of an article by Dawes et al. (1955b). There is also a striking diminution in the pulse-pressure, and a satisfactory method of measuring the diastolic pressure in babies might be expected to help in elucidating the changes in the functional capacity of the ductus. The characteristic precordial murmur described in lambs by Dawes et al. (1955a), and in babies by Burnard (1958), can also be used to study the changes in the ductus. We have made no systematic clinical or instrumental attempt to study this murmur, but the one baby in whom a murmur of this kind was loud enough to be detected in routine clinical observations is of some interest.

The baby was delivered by forceps on account of unexplained fœtal distress, and took 6 minutes to establish regular respirations. The cord was clamped 1 minute after delivery. The relationship between the development of the murmur and the recorded changes in systolic pressure is illustrated in fig. 3. This would presumably have been more informative had we been able to include measurements of the diastolic pressure. At the stage when the murmur was loudest the baby's colour was poor, with no obvious difference between arms and legs; but he was noted also to be abnormally cold at the time (rectal temperature 91·5° F). The rise in systolic pressure of 52 mm. Hg within the 1st week is the biggest rise we have observed in any of the 80 babies we have studied, and is nearly double the biggest rise recorded in a normal baby. It has also been

suggested to us by Dawes (personal communication) that the high systolic pressure present at birth may be caused by the chemical asphyxia which is known to be present even in clinically normal babies.

Tying the umbilical cord of the lamb causes an immediate rise in the systemic arterial pressure, amounting to between 4% and 46% of the initial level, with a mean of 19% (Dawes et al. 1953). In only 3 of our babies could we have expected to record such a rise; and the fact that we did so in only 1 of them might be explained by the fact that our observations were necessarily intermittent and a transient rise could have passed unrecorded. But Woodbury et al. (1938) also failed to detect any such rise, although they were using the direct method with continuous recording, and it seems unlikely that the immediate rise occurs in babies. In lambs, Born et al. (1956) attributed the immediate rise to the increase in peripheral vascular resistance. But Smith (1951) commented that the lamb " may have developed vaso-pressor mechanisms absent in certain other species (including the human) at birth ".

The delayed rise, reaching a peak $2^1/_2$–13 minutes after the cord has been clamped, which we have observed in 7 of the 12 babies whom we have studied, may have occurred in all of them but been missed because our observations were intermittent. A similar late rise in arterial pressure was noted by Born et al. (1956) when tying of the cord was followed by deliberate inadequate ventilation of the lungs resulting in anoxæmia. It does not seem likely that this was a factor in our babies, since by the time the cord was clamped they had a good colour, were breathing well, and had cried. Moreover, although we cannot be sure when the placenta separated, it seems likely that at least partial separation had occurred, and effective gaseous exchange across it had ceased, in the cases where the cord was clamped several minutes—20 minutes in 1 case—after the delivery had been completed. Perhaps the vasopressor mechanism postulated by Smith (1951) does exist in babies, but acts more slowly than in lambs.

Summary

In normal babies the systolic blood-pressure falls significantly during the first 24 hours of life. The range of the difference between the highest and lowest readings in 20 normal babies was 14–54 mm. Hg (mean 32).

Delay in clamping the cord, to enable blood to be transferred from the placenta to the baby's circulation, delays the fall, but does not affect its magnitude.

Clamping the cord has apparently no immediate effect; but in 7 of 12 cases studied there was a delayed rise in systolic pressure, reaching a peak $2^1/_2$–13 minutes after the cord was clamped.

REFERENCES

Ashworth, A. M., Neligan, G. A., Rogers, J. E. (1959) *Lancet*, i, 801.
Barcroft, J. (1946) Researches in Pre-natal Life; vol. 1, p. 113. Oxford.
Born, G. V. R., Dawes, G. S., Mott, J. C., Renwick, B. R. (1956) *J. Physiol.* **132,** 304.
Burnard, E. D. (1958) *Brit. med. J.* i, 806.
Dawes, G. S., Mott, J. C., Widdicombe, J. G., Wyatt, D. G. (1953) *J. Physiol.* **121,** 141.
— — — (1955a) *ibid.* **128,** 344.
— — — (1955b) *ibid.* p. 361.
Haselhorst, G. (1929) *Z. Geburt. und Gynäk,* **95,** 400.
Holland, W. W., Young, I. M. (1956) *Brit. med. J.* ii, 1331.
Schaffer, A. I. (1955) *Amer. J. Dis. Child.* **89,** 204.
Smith, C. A. (1951) The Physiology of the Newborn Infant; p. 102. Springfield, Ill.
Woodbury, R. A., Robinow, M., Hamilton, W. F. (1938) *Amer. J. Physiol.* **122,** 472.

BLOOD-VOLUME IN CHRONIC NUTRITIONAL ANÆMIA

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THE changes which take place in the plasma and blood-volume after acute blood-loss and in shock have been extensively studied, but there is surprisingly little information on the changes in chronic anæmia. This applies particularly where the anæmia is severe—that is, with a hæmoglobin concentration of less than 4 g. per 100 ml.

Boycott (1911), using the carbon-monoxide method, found a greatly raised plasma-volume in three patients with moderate hookworm anæmia.

Keith et al. (1915), using a dye method, studied ten patients with anæmia and emaciation and found normal plasma-volumes. Of three other patients with pernicious anæmia they found the plasma-volume to be normal in two, but raised in the third. Later, Keith (1923) found in twenty-four patients, with either pernicious anæmia or leukæmia, that the plasma-volumes were either normal or increased and the blood-volumes either normal or reduced; in leukæmia the blood-volume was usually increased.

Denny (1921) studied ten patients with pernicious anæmia and found the blood-volume to be decreased in eight of them, but the plasma-volume was essentially normal.

de Wesselow and Bamforth (1928) found, in eight patients with pernicious anæmia, that the plasma-volume was constant in the individual patient as the anæmia improved with treatment. However, Gibson (1939) and Gibson et al. (1939), after an extensive study of different types of chronic anæmia, concluded that the plasma-volume was much increased, although the blood-volume was reduced because of the decreased red-cell volume.

More recently, McMichael et al. (1943) found that the blood-volume in twenty-four patients with various types of chronic anæmia was much reduced. Allington and Taylor (1955) also studied the plasma-volume changes in six patients with pernicious anæmia during treatment; in four there was no significant change, but two showed an increase.

Using a different approach, Rabiner and Lichtman (1957) studied the red-cell volume with ^{32}P in thirteen patients with pernicious anæmia. They concluded that there was a poor correlation between the packed-cell volume and total circulating red-cell volume, presumably owing to changes in the plasma-volume.

There appears to be fairly general agreement that the blood-volume tends to fall in chronic anæmia, but less agreement on the changes that take place in the plasma-volume.

This paper presents results of plasma and blood volume studies on seventy-four patients, who were either hæmatologically normal or had chronic nutritional anæmia, some with a hæmoglobin level of less than 2 g. per 100 ml.

Material and Methods

The patients studied were admitted to the General Hospital, Kuala Lumpur. They were all adults; a few were pregnant women, and some had severe malnutrition. The anæmia was either of the nutritional megaloblastic type or due to an iron deficiency, the latter often associated with hookworm infection.

The studies of the blood were all undertaken at about 9 A.M. The hæmoglobin level was estimated by the cyanhæmatin method. The packed-cell volume was determined by centrifugation at 3000 r.p.m. in a Wintrobe tube for thirty minutes. Both estimations were done in triplicate. The plasma-volume was estimated by measuring 5 ml. of an 0·5% solution of Evans-blue in physiological saline solution from a pipette, injecting and washing the dye through a three-way tap system.

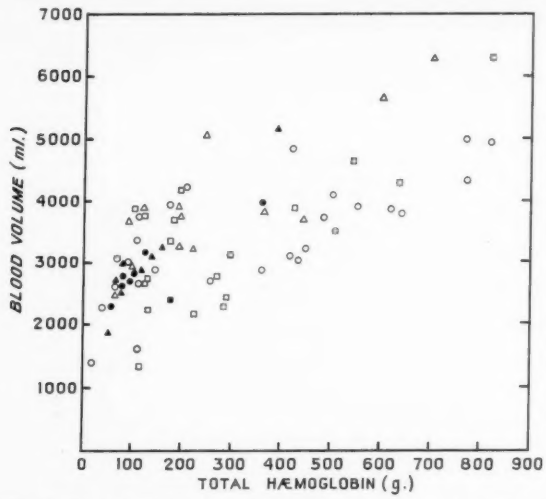

Fig. 1—Relation of the blood-volume to the total circulating hæmoglobin.

○ Normal and iron-deficient patients.
△ Pregnant women, either normal or with iron-deficiency anæmia.
□ Patients with severe malnutrition.
● Patients with megaloblastic anæmia.

A single blood sample was taken ten minutes later for measurement of the dye concentration in the serum.

In view of the small and uncertain amount of the plasma trapped in the red-cell column of the hæmatocrit tube, the reading of the packed-cell volume was not corrected for this factor. It was, however, multiplied by 0·91 as a correction for the ratio between the peripheral blood and body hæmatocrit (Chaplin et al. 1953) before using the value to calculate the red-cell volume.

The values obtained were not then corrected for body-weight, as it was found that this did not reduce the scatter of points.

Results and Discussion

Fig. 1 relates the blood-volume to the total circulating hæmoglobin. This figure shows that the blood-volume falls with the drop in hæmoglobin. As might be expected, the pregnant women tended to have blood-volumes on the higher side of the slope. In contrast many of the severe malnourished patients showed values on the lower side. This might be due to dehydration, as some of these patients had had diarrhœa.

When the plasma-volume was related to the total circulating hæmoglobin, no correlation was found. Thus the drop in blood-volume with increasing anæmia was almost wholly due to the diminution in the red-cell volume.

Any effect of a change in plasma-volume with increasing anæmia can be demonstrated more usefully. Fig. 2 relates the packed-cell volume to the circulating red-cell volume.

If the blood-volume remained constant as the red-cell volume decreased—that is, the plasma-volume increased progressively to make up the deficit—there would be a straight-line relationship between the packed-cell volume and the red-cell volume. The packed-cell volume, which is a concentration, would measure accurately the total red-cell volume. This line must pass through the origin. A practical upper point was calculated from the present data by taking the mean values for these two variables as they were actually found in the fourteen patients who had a total circulating hæmoglobin greater than 480 g. per 100 ml., and the straight line was drawn as shown in fig. 2. As the anæmia worsens, the points tend to rise above this line.

If, however, the plasma-volume is assumed to remain constant—that is, the blood-volume to fall progressively by an amount equal to the loss of red-cell volume—the relationship becomes curved. A second practical curve was calculated by assuming that the plasma-volume remained constant at the mean value (1920 ml.) found for the upper fourteen patients and adding increasing increments of red-cell volume of between 150 ml. and 2500 ml. to make up the total blood-volume. The expected packed-cell volume for each value of red-cell volume was then readily calculated to give the curve shown. This curve follows closely the trend of the actual points.

A similar relationship must exist between the hæmoglobin level and total circulating hæmoglobin. This is shown in fig. 3. In this case, when calculating the curve it was necessary to assume that the mean corpuscular hæmoglobin concentration remained at the mean value of 33·4% that was found in the upper fourteen patients. The points representing the pregnant women tend to lie on the lower side, again because of the relatively increased plasma-volume, while those of the malnourished patients lie on the upper side.

When the hæmoglobin level falls below about 3 g. per 100 ml., equivalent to roughly 75 g. total hæmoglobin, the points show a slight tendency to rise higher than the curve, indicating a possible decrease in plasma-volume. This degree of anæmia is only just compatible with life, and the severe circulatory changes which are evident might account for this apparent decrease in plasma-volume.

Because the plasma-volume remains essentially constant, the hæmoglobin level reads high in the anæmic patients when compared with the total circulating hæmoglobin. Thus, in fig. 3, when 100 g. of hæmoglobin is circulating the expected level is 2·2 g. per 100 ml., but the actual value found is nearer 3·3 g. per 100 ml., which is 50% higher. This percentage error increases as the anæmia becomes more severe.

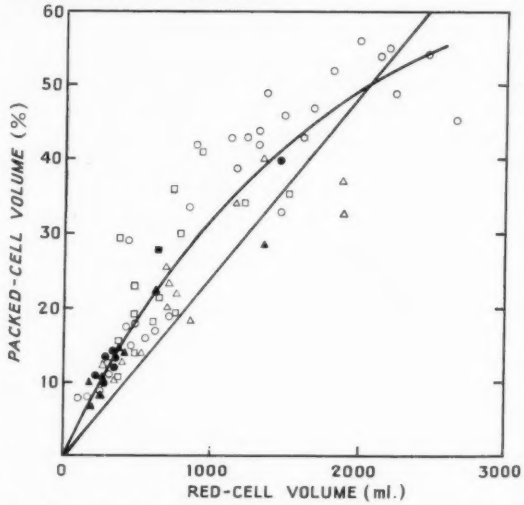

Fig. 2—Relation of packed-cell volume to circulating red-cell volume. The straight line indicates the association that would be expected if the blood-volume remained constant, the curved line if the plasma-volume remained constant. Symbols as in fig. 1.

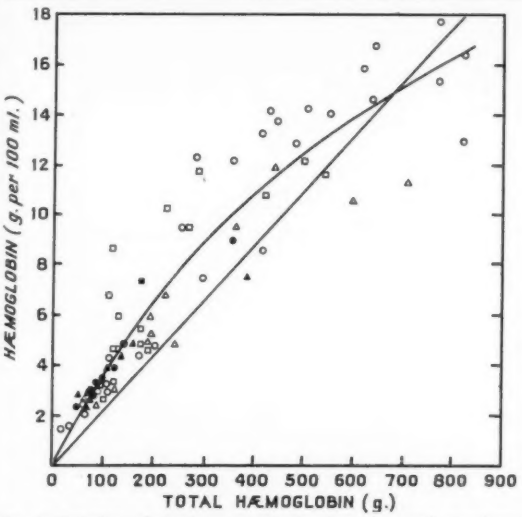

Fig. 3—Relation of the hæmoglobin level to the total circulating hæmoglobin. Symbols as in fig. 1.

The power of the blood to transport oxygen depends both on the total amount of hæmoglobin circulating and on its level in the blood. As the total decreases, the diminution in blood-volume keeps the level as high as possible, so assisting the ability to carry oxygen when the need increases.

Summary

The plasma-volume, red-cell volume, blood-volume, and total circulating hæmoglobin were estimated in seventy-four patients with chronic nutritional anæmia.

While the blood-volume decreased progressively with intensification of the anæmia, the plasma-volume remained essentially constant, the drop in blood-volume being largely accounted for by the reduction in red-cell volume.

Hence, as the anæmia became more severe, the hæmoglobin level read progressively too high when compared with the total circulating hæmoglobin. In the most severe degrees of anæmia the error was as much as 50% too high.

REFERENCES

Allington, M. J., Taylor, W. H. (1955) *Brit. J. Hæmat.* **1**, 241.
Boycott, A. E. (1911) *Lancet*, i, 717.
Chaplin, H., Mollison, P. L., Vetter, H. (1953) *J. clin. Invest.* **32**, 1309.
Denny, G. P. (1921) *Arch. intern. Med.* **27**, 38.
de Wesselow, O. L. V., Bamforth, J. (1928) *Lancet*, i, 1067.
Gibson, J. G. (1939) *J. clin. Invest.* **18**, 401.
— Harris, A. W., Swigert, V. W. (1939) *ibid.* p. 621.
Keith, N. M. (1923) *Amer. J. med. Sci.* **165**, 174.
— Rowntree, L. G., Geraghty, J. T. (1915) *Arch. intern. Med.* **16**, 547.
McMichael, J., Sharpey-Schafer, E. P., Mollison, P. L., Vaughan, J. M. (1943) *Lancet*, i, 637.
Rabiner, S. F., Lichtman, H. C. (1957) *Arch. intern. Med.* **99**, 474.

"... Man's reproductive impulses have been evolved as an adaptation to circumstances in which the odds against him were so great that only a small proportion of the human race survived to reproduce the next generation. Now all that has suddenly changed, as a result of scientific discoveries which were made and applied because they were good in themselves, and without any co-ordinated consideration of their probable consequences. Man has interfered with his own evolution so effectively that disaster awaits him unless he can show equal intelligence and co-operation to avert the results of his action, for unless birth control can be applied on the same scale as death control there is every likelihood that within a generation the world's population will outrun its means of subsistence."—Sir RUSSELL BRAIN in *Science, Philosophy, and Religion* (Eddington lecture, 1959). London: Cambridge University Press.

HISTONE: AN ESSENTIAL COMPONENT FOR THE LUPUS ERYTHEMATOSUS ANTINUCLEAR REACTION

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THE sera of patients with systemic lupus erythematosus (and some related conditions) contain globulins with affinity for cell nuclei and for some of their separate components. The immunological features of these phenomena have recently been reviewed by Seligmann (1958), and quantitatively investigated by Deicher et al. (1959). We have previously demonstrated (Holborow, Weir, and Johnson 1957) in the sera of these patients a factor with affinity for somatic cell nuclei of many species. In the present work we report the failure of this factor to react with the nuclear material of mature guineapig spermatozoa, although the precursor germ-cell nuclei take up the factor strongly.

The uptake of antinuclear factor by cell nuclei was demonstrated in tissue sections by a fluorescent anti-globulin serum (Coons and Kaplan 1950) as previously described by us (Holborow, Weir, Johnson 1957). Fresh frozen sections of guineapig testis and epididymis were used.

Results

When sections were treated with normal human serum followed by anti-globulin fluorescent conjugate, no nuclear staining occurred (fig. 1). With 11 human sera known to

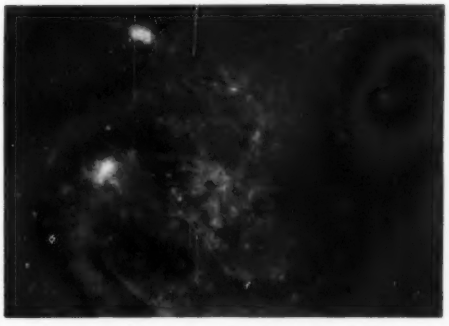

Fig. 1—Section of guineapig testis showing seminiferous tubule treated with normal serum. No nuclear staining after treatment with anti-human globulin conjugate (×210).

contain antinuclear factor, the nuclei of the somatic cells and the immature germ-cells (spermatogonia and spermatocytes) in the testis became fluorescent (fig. 2), but the heads of the mature sperm did not. In the epididymis, only the epithelial lining cells showed nuclear fluorescence, the sperm heads remaining unstained.

Vendrely et al. (1957) have shown that at the end of the maturation process in spermatogenesis nucleohistone is transformed to a protamine-like substance. Several workers have suggested that nuclear histone is involved in the reactions between "L.E. globulins" and nuclear material (Godman and Deitch 1957, Holman and Kunkel 1957, Bardawil et al. 1958, Friou 1958). The present work shows directly that mature spermatozoa lack an essential component for the antinuclear reaction. This observation,

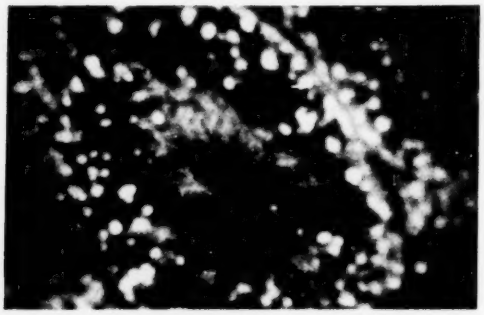

Fig. 2—Same tissue as fig. 1 treated with serum positive for the antinuclear factor followed by conjugate. Note specific staining of all cell nuclei except spermatozoa (×210).

taken in conjunction with the work of Vendrely et al. (1957), provides strong presumptive evidence that this component is histone.

One of us (D. M. W.) is in receipt of a grant from the Empire Rheumatism Council.

REFERENCES

Bardawil, W. A., Toy, B. L., Galins, N. (1958) *Lancet*, i, 888.
Coons, A. H., Kaplan, M. H. (1950) *J. exp. Med.* **91**, 1.
Deicher, H. R. G., Holman, H. R., Kunkel, H. G. (1959) *ibid.* **109**, 97.
Friou, G. J. (1958) *J. Immunol.* **80**, 476.
Godman, C. G., Deitch, A. D. (1957) *J. exp. Med.* **106**, 593.
Holborow, E. J., Weir, D. M., Johnson, G. D. (1957) *Brit. med. J.* ii, 732.
Holman, H. R., Kunkel, H. G. (1957) *Science*, **126**, 162.
Seligmann, M. (1958) *Rev. fr. clin. biol.* **3**, 558.
Vendrely, R., Knobloch, A., Vendrely, C. (1957) *Exp. Cell Res.* **13** (suppl. 4), 279.

REACTION OF GUINEAPIG SPERMATOZOA WITH HOMOLOGOUS ANTIBODY
AS DEMONSTRATED BY FLUORESCENT STAINING

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IF homologous testis or sperm in Freund's adjuvant (Freund et al. 1953) is injected into guineapigs, circulating antibodies are produced which will immobilise sperm (Metalnikoff 1900). If serum containing these antibodies is added to preparations of testis or sperm, histamine will be released (Baum, Monger, and Schild 1959).

We have found that such antibodies react with the heads of mature guineapig spermatozoa, but not with the precursor germ-cells. Their uptake of the antibodies was demonstrated in fresh frozen sections of guineapig testis and epididymis by treatment with a fluorescent anti-guineapig globulin serum (see the preceding paper).

When sections were treated with normal guineapig serum followed by anti-guineapig fluorescent conjugate, no staining occurred. A similar appearance is seen in fig. 1 of the preceding article by Holborow and Weir. When similar sections were stained with serum from a guineapig sensitised with homologous testis, the somatic cells and the immature germ-cells in the testis did not stain, but the heads of the mature sperm in the central part of the seminiferous tubule became fluorescent (fig. 1). In the epididymis there was fluorescence of the heads of the spermatozoa, but not of the epithelial lining cells (fig. 2).

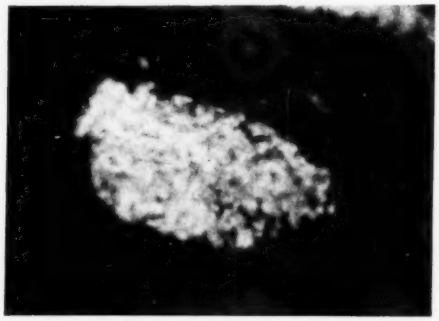

Fig. 2—Section of epididymis of guineapig treated as in fig. 1 showing fluorescence of packed sperm.

L.E. serum is believed to react with nuclear material containing histone as the nucleoprotein. Holborow and Weir (1959) found that this serum stained spermatogonia and spermatocytes but did not stain mature sperm, and Vendrely et al. (1957) have shown that at the end of spermatogenesis there is a transformation of histone into a protamine-like substance. Taken together these various observations are presumptive evidence that in guineapigs sensitised with homologous testis, the antibody is directed against material peculiar to the end stages of spermatogenesis, namely protamine.

REFERENCES

Baum, J., Monger, J. L., Schild, H. O. (1959) *J. Physiol.* (in the press).
Freund, J., Murray, M. L., Thompson, G. E. (1953) *J. exp. Med.* **97**, 711.
Holborow, E. J., Weir, D. M. (1959) *Lancet*, i, 809.
Metalnikoff, S. (1900) *Ann. Inst. Pasteur*, **14**, 577.
Vendrely, R., Knobloch, A., Vendrely, C. (1957) *Exp. Cell Res.* **13**, suppl. 4, 279.

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Fig. 1—Section of seminiferous tubule of guineapig testis. Note the fluorescence of mature sperm, in central area of tubule, after treatment with sensitised guineapig serum and conjugate.

". . . The patient does not get so much nursing in the United States as in the United Kingdom. . . . One corollary of understaffing in the United States (by British standards) is that it underlines and emphasizes the over-all authority of the resident in the wards. Another is that the wards usually look untidy by British standards. This could hardly be otherwise in the face of the amount of patient disturbance that the American system involves. Sometimes, I think that British wards are too spick-and-span and that this appearance can only be achieved at the expense of inadequate contact between the patient and those responsible for his medical care. Here is a point at which compromise between the two systems might be valuable. Meanwhile, one will continue to find in both countries a proportion of patients who feel too ill to go into the hospital, fearing on the one side of the Atlantic the regimentation of a powerful nursing tradition and on the other the exsanguinating effects of over-investigation."—Dr. J. F. STOKES, *New Engl. J. Med.* Jan. 8, 1959, p. 260.

PHÆOCHROMOCYTOMA IN PREGNANCY

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A PHÆOCHROMOCYTOMA, a rare tumour of the adrenal medulla, produces noradrenaline and adrenaline and seems sometimes to be awakened into activity at times of endocrine development. It is therefore not surprising that such tumours should arise in pregnancy, but so far only 33 of them have been diagnosed in association with pregnancy. 16 of these resulted in the death of the mother, usually shortly after delivery. These deaths might have been prevented had there been a wider appreciation of the condition and an earlier diagnosis.

Of these two patients described here, the first died suddenly in the antepartum period, and the second we believe is the only one recorded in which diagnosis and operation in the antenatal period has been followed by spontaneous delivery of a live baby.

Case-records

Case 1.—This patient, aged 29, first noticed attacks of blurred vision in November, 1951. These subsided but in July, 1952, faintness, palpitation, and vomiting developed. A tachycardia was noticed together with a tremor and some thyroid enlargement. Her blood-pressure was 200/110 mm. Hg, and on another occasion 130/80, but the symptoms were attributed to hyperthyroidism.

On Feb. 5, 1953, she was seen by her own doctor when 30 weeks pregnant. Her blood-pressure was then 138/80, there was some albuminuria, and she complained of the recent onset of headaches. The size of the uterus corresponded to a 28-week pregnancy. A few days later there was still a trace of albuminuria and the blood-pressure was again 138/80. It fluctuated for the next two weeks, but on Feb. 19 it rose to 150/90 with no albuminuria. She was then admitted. By this time, although she felt movements, the fœtal heart could not be heard and fœtal death was assumed. The blood-pressure fluctuated tremendously during the next eleven days, rising to peaks of 250/130 and at other times falling to 130/85, in spite of the fact that the fœtus was obviously dead. The urine never contained more than a trace of albumin, but on four successive days reduced Benedict's solution to a yellow or orange colour. She was sedated heavily with amylobarbitone without any effect on the blood-pressure. She looked and felt well until March 1, when she suddenly vomited twice, collapsed, and died within a few minutes.

The postmortem revealed a phæochromocytoma of the left adrenal gland, and a macerated fœtus of about 28 weeks' gestation. The immediate cause of death was a hæmorrhage into the tumour.

Case 2.—This patient, aged 29, had had three normal full-term pregnancies, resulting in three live children weighing from 8 lb. to 8 lb. 13 oz. Her blood-pressure had been recorded throughout all three pregnancies and had only varied from 110/70 to 120/80 and had never risen above this figure.

She was under the care of her own doctor in the fourth pregnancy and on July 11, 1957, when she was 12 weeks pregnant, he found a blood-pressure of 130/80: there was no albuminuria, and her weight was 9 stone. She failed to keep her next appointment, but called on him on Oct. 3 because of blurring of vision, suggesting she wanted new glasses. The blood-pressure was 180/140; there was no albuminuria and her weight had risen to 10 stone. He sent her into hospital straight away. Since August she had gradually developed

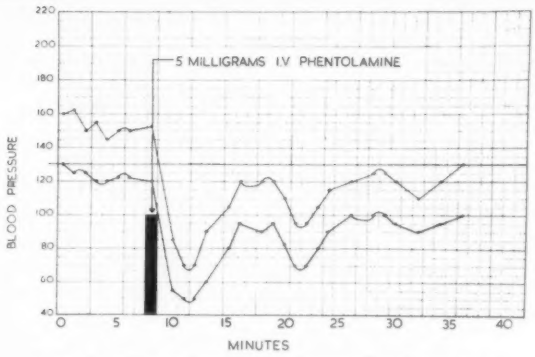

Fig. 1—Effect of intravenous phentolamine in case 2.

severe headaches in the daytime. She had not previously suffered from headaches, but these were severe enough to send her to bed on several occasions. She was also troubled by sweating attacks which lasted about ten minutes, mainly after getting out of bed in the morning. They were unrelated to the headaches. Two weeks before admission she fainted early one morning when leaving her bed. The blurred vision had also developed over several weeks and by the time of admission it was so bad that she could barely read her shopping-list.

She was neither flushed nor abnormally pale. The ocular fundi showed papillœdema, extensive hæmorrhages, and exudates (grade-IV retinopathy). No abnormality was found in the heart or lungs; the femoral pulses were normal, and there was no œdema. The size of the uterus corresponded to a 24-weeks pregnancy. The pulse-rate was 128 and the blood-pressure 180/130. The urine contained no albumin, sugar, casts, or red cells. The blood-urea was 15 mg. per 100 ml., hæmoglobin 82%, and white cells 18,600 per c.mm. (76% polymorphs). An electrocardiogram was normal, apart from a sinus tachycardia of 125.

At first her condition was thought to be due to toxæmia of pregnancy, and she was sedated with amylobarbitone. The blood-pressure remained at about 170/130, with no gross fluctuation. Mecamylamine was given, 2·5 mg. twice daily. Sweating became more frequent and postural hypotension developed—90/70 on one occasion. The average blood-pressure came down to 140/100 even though the dose was reduced to 1·25 mg. daily.

Because of the severity of the blood-pressure at the sixth month of pregnancy and the extreme sensitivity to a ganglion-blocking drug, further tests were undertaken. 5 mg. of phentolamine intravenously produced a dramatic fall in blood-pressure and a feeling of faintness and flushing, followed in a few minutes by pallor and profuse sweating (fig. 1). A 24-hour specimen of urine contained 5·5 mg. of noradrenaline with no detectable amounts of adrenaline. Intravenous pyelography was normal. These tests indicated a phæochromocytoma. The blood-pressure rose to 190/160 and on several occasions phentolamine was given by injection in order to lower this dangerously high level.

On Oct. 24 a perirenal air insufflation was done by Dr. F. G. M. Ross and regarded as normal although there was a rounded shadow above the left kidney (fig. 2). On Oct. 25 she had an attack of acute pulmonary œdema which responded to morphine, aminophylline, and phentolamine. This episode emphasised the severity of the condition and the need to operate before term. Treatment with phentolamine, by mouth and intramuscularly, digoxin, and 'Neptal' was continued. On Oct. 29, twenty-six days after admission, Prof. R. Milnes Walker exposed a left-sided tumour of the adrenal gland, through a midline incision. After preliminary clamping of the draining veins, it was removed. There was an immediate fall in blood-pressure, and intraveous hydrocortisone and noradrenaline were necessary for two days to keep the pressure normal. Her convalescence was otherwise uneventful

and she was discharged home on Nov. 13 with a blood-pressure of 110/78 and pulse-rate of 76.

The tumour was yellowish-brown, weighed 38 g., and measured 3×3×2 cm. (fig. 3) The constituent cells were large and pleomorphic with large nuclei and well-marked nucleoli but no evidence of malignancy. Biological estimation of the catechol amines in the tumour revealed a content of 21 mg., of which 98·5% was noradrenaline.

She was seen again on Dec. 13, when she was feeling very well. Her vision was now normal, although hard exudates were still visible in the fundi, and the blood-pressure was 140/100. The uterus corresponded to the dates of 34–35 weeks' gestation with a single living vertex presentation. On Dec. 18, when she was about 35 weeks pregnant, she went

Fig. 2—Tomogram of kidneys after perirenal air insufflation showing rounded shadow overlying upper pole of left kidney.

into labour. After a first stage of three hours and a second stage of five minutes, with a blood-pressure varying from 130/90 to 140/110, she was delivered of a living female child weighing 5 lb. 4 oz. In the puerperium, the blood-pressure varied from 110/70 to 125/90. She was discharged on Jan. 10, 1958, with a blood-pressure of 115/80. After birth, the baby became slightly jaundiced and showed evidence of ABO incompatibility but responded to treatment in the premature-baby unit. On discharge she weighed 5 lb. 12 oz. and was fully breast-fed.

The patient has remained well and when last seen in June, 1958, the blood-pressure was 125/80; visual acuity was normal but many retinal scars remained.

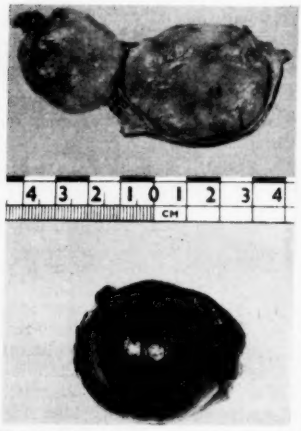

Fig. 3—Phæochromocytoma removed in case 2.

Discussion

Gemmell (1955) reviewed the problem of diagnosis of phæochromocytoma in 212 women and found that symptoms were related to pregnancy in about 30% of them. Dean (1958) collected 32 examples from the literature where the condition was diagnosed in relation to pregnancy and recorded a 50% mortality: many fatalities occurred within a day of delivery from a hypertensive crisis. Only three patients have so far been reported in which diagnosis and removal of the tumour before delivery led to a successful outcome for mother and child. Keir (1955) found a tumour during a cæsarean section and removed it ten months later when the patient had again become pregnant: the patient delivered a normal child six months afterwards. Dean (1958) diagnosed the condition at the 38th week of pregnancy and removed the tumour at the time of a cæsarean section. Our case 2 is only the third in the literature in which the tumour has been successfully removed during pregnancy.

Most of the deaths follow soon after delivery from a hypertensive crisis leading to ventricular fibrillation or cerebral hæmorrhage. Our first case illustrates that sudden death can occur even in the antepartum period. Our second case shows the importance of diagnosis and removal of these tumours during pregnancy. She had an attack of acute pulmonary œdema a few days before the operation, and would probably have died before or shortly after term without this intervention.

A phæochromocytoma should be suspected in any patient with a labile hytertension or a sustained hypertension with crises. These crises often cause headaches, sweating, flushing, palpitation, or blurred vision. They may be provoked by general anæsthetics, labour, and even changes in posture, as in our case 2, where attacks occurred on first rising in the morning. Perirenal air insufflation may also cause a hypertensive crisis, as in our second patient. The presence of these tumours is best confirmed by urinary estimation of catechol amines and the hypotensive action of phentolamine.

Summary

Two examples of phæochromocytoma during pregnancy are reported. In one, sudden death ensued; in the other the tumour was removed successfully and spontaneous delivery of a live baby followed two months later.

We wish to thank all our colleagues who assisted in the diagnosis and treatment, in particular Prof. R. Milnes Walker.

REFERENCES

Dean, R. E. (1958) *Obstet. Gynec.* **11**, 35.
Gemmell, A. A. (1955) *J. Obstet. Gynæc. Brit. Emp.* **62**, 195.
Keir, F. E. (1955) *J. Internat. Coll. Surg.* **24**, 316.

NEUROMUSCULAR-BLOCKING ACTION OF STREPTOMYCIN

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IT has been shown experimentally that neomycin in normal doses and streptomycin in large doses may produce neuromuscular block (Foldes 1958). There does not seem to be a recorded instance of streptomycin producing this curare-like effect, as in the following three cases.

Case 1.—A married woman, aged 44, with bacterial endocarditis, received streptomycin 1 g. daily for 28 days. She complained of extreme muscular weakness and of progressive inability to sew or read small print. She was unable to stand unaided, and on Snellen's test card her vision was 6/12–6/18 in

both eyes. Neostigmine 1·5 mg. and atropine 0·6 mg. were given intravenously, and 5 minutes later her vision was 6/6 in both eyes and she could stand and walk a few steps. The effect of the neostigmine wore off in about 40 minutes. Streptomycin therapy was stopped, and within 48 hours her muscular weakness and visual difficulty had finally disappeared.

Case 2.—A man, aged 60, had undergone excision of the ischiorectal fossa with a pedicle skin graft, which were followed by repeated small superficial abscesses in the same area. Streptomycin 1 g. daily was started and continued for 3 months, during which the patient remained free from abscesses. He complained, however, of such muscular weakness, especially in the evenings, that the streptomycin was stopped. A week later a further abscess developed in his perineum and had to be surgically drained. Streptomycin 1 g. daily was resumed, and he was given neostigmine by mouth. Muscular weakness soon developed and did not disappear until 30 mg. neostigmine by mouth daily was given. He has satisfactorily continued on this for 9 months.

Case 3.—A man, aged 62, had received streptomycin 1 g. daily for 3 days after appendicectomy on account of acute appendicitis with severe peritonitis. On the 3rd postoperative day he was still very ill and complained of severely blurred vision; he was unable to distinguish the number of fingers held up at the bottom of his bed. He was given neostigmine 1 mg. and atropine 0·6 mg. intravenously, and 2 minutes later he could read the bed number written on the wall over the head of the bed on the opposite side of the ward. Streptomycin therapy was stopped.

Discussion

As no cases of this curare-like side-effect of streptomycin have been recorded it is presumably rare. Inquiry at a sanatorium where many patients have been given streptomycin revealed that no cases of muscular weakness had been noticed; but many instances of visual disturbance had been noted, and this had always been taken as a toxic manifestation of streptomycin and as an indication to stop the drug.

The condition can be established with certainty by administering intravenous neostigmine 1–1·5 mg., with atropine 0·6 mg. to prevent bradycardia, when the muscular weakness and visual disturbance will stop at once.

Although these changes are only temporary, and are in no way similar to the permanent palsy of the 8th cranial nerve which streptomycin can produce, it is probably wise to stop the drug when they arise. When, however (as in case 2), this is impracticable, then neostigmine can be given by mouth as in myasthenia gravis.

We should like to thank Mr. D. W. Bracey and Mr. B. C. Rowlands, consultant surgeons, for allowing us to publish details of cases 2 and 3.

REFERENCE

Foldes, F. F. (1958) *Anæsthesia*, **13**, 191.

POSTPARTUM PANCREATITIS WITH URTICARIA

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SINCE Haidlen described pancreatitis after pregnancy in 1884 the syndrome has been reported by many workers (Langmade and Edmondson 1951, Joske 1955). As far as we know, acute urticaria has not been noted as an accompaniment of this condition; and we therefore present the following case in which acute urticaria complicated pancreatitis after pregnancy.

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Case-record

A woman, aged 20, was admitted to hospital on March 26, 1958, with acute generalised urticaria of three hours' duration. Six weeks previously she had been delivered of a full-time healthy infant. Since then she had experienced short attacks of colicky upper abdominal pain; and she had had such an attack the day before the onset of urticaria. There was no history of any medication, nor had she partaken of unusual food.

On admission temperature and pulse were normal, and the blood-pressure (B.P.) was 120/75 mm. Hg. There was generalised urticaria with severe œdema of the face, especially the eyelids. Abdominal palpation elicited only slight tenderness in the right hypochondrium. The patient was constipated. White blood-cells 8500 per c. mm.; no eosinophilia. Fæces of normal colour; no parasites. Diphenhydramine ('Benadryl') 50 mg. q.i.d. was prescribed for the unexplained urticaria.

Course.—On the following day the patient vomited several times and had epigastric pain. Her temperature rose to 100·2 F and her pulse-rate to 100 per minute. Promethazine ('Avomine') was given but vomiting continued. The urticaria progressively diminished and by evening had almost disappeared. Vomiting persisted throughout the night, and on March 28 the patient looked shocked and was having constant epigastric pain. The B.P. remained at 120/75. The electrocardiogram was normal. Serum-amylase 3200 Somogyi units per ml.; serum-bilirubin 1·75 mg. per 100 ml.; plasma-proteins 6·05 g. (albumin 3·6 g., globulin 2·45 g.) per 100 ml.; serum-alkaline-phosphatase 11 King-Armstrong units; thymol turbidity 2 units; cephalin flocculation +. Acute pancreatitis was diagnosed.

The patient was treated with atropine and morphine.

On March 29 the serum-amylase was 6400 Somogyi units per ml.; the patient was still vomiting, and there was a recurrence of urticaria on the arms. Chlortetracycline therapy was started (1 g. daily in divided doses). On the next day the temperature and pulse-rate remained elevated and the patient still looked ill, but the urticaria had disappeared. Serum-amylase 800 Somogyi units per ml.; serum-lipase 1·1 ml. *N*/20 NaOH per ml. of serum; serum-calcium 8·8 mg. per 100 ml.; serum-cholesterol 130 mg. per 100 ml.; fasting blood-sugar 87 mg. per 100 ml. Thereafter the symptoms gradually abated, and all therapy was discontinued on April 4.

Subsequent investigations.—Straight X-ray of the abdomen did not reveal any pancreatic calcification. A cholecystogram showed good concentration with iopanoic acid ('Telepaque'); at least three small non-opaque stones were seen in the gall-bladder. 'Biligrafin' outlined a common bileduct of normal calibre, and after a fatty meal the contrast medium flowed freely into the duodenum.

Discussion

There is no doubt that this patient experienced an attack of acute pancreatitis which was clinically manifest twenty-four hours after the onset of acute urticaria. Visceral lesions (Chevallier 1936) and myocardial changes (Foster and Laymann 1952, Rogen 1957) have been reported in association with urticaria. In the present case the urticaria may have been secondary to the acute pancreatitis; it seems possible that involvement of the pancreatic duct by the urticaria led to the pancreatitis.

We thank Dr. J. Rogers for permission to report this case and for helpful advice.

REFERENCES

Chevallier, P. (1936) *Ann. Derm. Syph.* **7**, 113.
Foster, R. F., Layman, J. A. (1952) *J. Amer. med. Ass.* **148**, 203.
Haidlen, R. (1884) *Zbl. Gynäk*, **8**, 608.
Joske, R. A. (1955) *Brit. med. J.* i, 124.
Langmade, C. F., Edmondson, H. A. (1951) *Surg. Gynec. Obstet.* **92**, 43.
Rogen, A. S. (1957) *Scot. med. J.* **2**, 407.

Preliminary Communications

THE EFFECT OF MAGNESIUM ON BLOOD COAGULATION IN HUMAN SUBJECTS

SMALL amounts of magnesium added to fresh unclotted human plasma prolong the clotting-time considerably.[1] This action was explained by a cation antagonism between Mg^{++} and Ca^{++}, both competing for combination with clotting factors. Such ion antagonism had been demonstrated in muscle and in nerve end-plates where the breakdown of adenosine triphosphate is activated by Ca^{++} in muscle and by Mg^{++} in end-plates.[2] The quantity of magnesium needed to produce this in-vitro effect was about ten times the normal plasma level. Several attempts have been made to test this action of magnesium in vivo, notably in Germany where, during and shortly after the 1939–45 war, magnesium sulphate was widely used as a muscle relaxant. It was seen that the blood of patients examined post mortem after such treatment was unclotted. Schnitzler[3] summarises these experiences in his report on the use of 200 mg. of magnesium given three times daily, post partum, to prevent thrombosis. We have not been able to confirm his results, which indicated a highly significant prolongation of the whole-blood clotting-time after a single dose of 300 mg. of magnesium. Malkiel-Shapiro et al.[4] claimed that they improved the clinical status of patients with coronary disease when they administered magnesium parenterally. This they related to an interaction between Mg^{++} and serum-lipids rather than to an effect of the Mg^{++} on the coagulation mechanism. Brown et al.[5] were unable to find such a relation between Mg^{++} and lipids in health or in disease.

We investigated the effect on clotting-time of the ingestion of 1 g. of magnesium. The magnesium was given to adult volunteers as the citrate in about 100 ml. of water. There were suggestive results when the clotting-time was measured by the Lee and White method before the dose and after 1, 2, and 3 hours. It was then decided to modify the test in two ways:

(1) Though magnesium citrate is soluble, when taken by mouth some of the magnesium will probably be rendered insoluble. Aminoacids are known to increase the solubility of sparingly soluble salts of divalent cations [6] and the ingestion of protein increases the absorption of such salts.[7] We administered, therefore, 50 g. of peptone with 1 g. magnesium (as citrate). This procedure led more regularly to prolongation of clotting-time (Lee and White); but duplicate results of that method vary so much that significant evidence would require statistical analysis of many experiments.

(2) At the suggestion of Dr. R. G. Macfarlane we therefore used the whole-blood thrombin-generation test rather than the Lee and White technique to measure changes in the coagulation process.[8]

EXPERIMENTAL PROCEDURE

5 ml. of blood, withdrawn cleanly by venepuncture into a siliconed syringe, were placed into an unsiliconed flat-bottomed glass bottle of about 30 ml. capacity (" universal container "). The bottle was already immersed in a water-bath at 37°C. A stop-watch was started the moment blood appeared in the syringe. Into each of a series of small glass test-tubes (50 × 10 mm.) immersed in the water-bath was pipetted 0·2 ml. of 0·2% bovine fibrinogen solution made up in saline buffered at pH 7·2 by Owren's barbitone buffer. After 10 minutes samples of 0·2 ml. of blood were withdrawn from the incubating bottle at intervals of 1 minute and added to the fibrinogen. The clotting-time of each fibrinogen tube was recorded and plotted against the time of incubation of the whole blood. After 10 minutes of incubation the clotting-time of the fibrinogen usually exceeds 2 minutes and within 12–16 minutes it reaches a minimum of about 7 seconds. This represents the peak of thrombin generation. Magnesium and peptone were then taken and the procedure was repeated 1 hour after the dose. All measurements were carried out in duplicate.

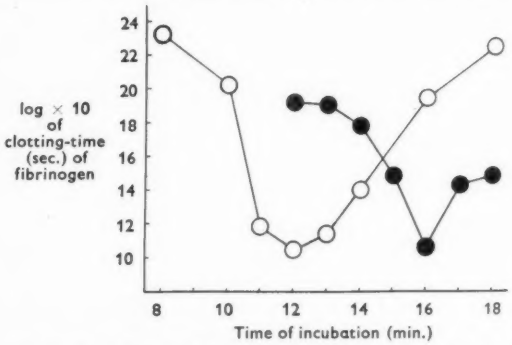
All glassware was immersed for 24 hours in chromic and sulphuric acid, washed 10 times in distilled water, then dried by autoclaving for 1 hour at 150°C. It is particularly important that the glassware should at no time have been in contact with anionic detergents.

RESULTS

The experiments were performed on 10 adults (9 male and 1 female). When 1 g. Ca^{++} (as the chloride) was taken with the magnesium-peptone mixture no shift in the peak of thrombin generation occurred (2 experiments). On 2 occasions the taking of a sandwich meal shortly after the magnesium and peptone had been ingested was associated with a failure of the experiment. It was decided, therefore, that the subject should be fasting for 1 hour before and after the dose. Nevertheless 1 out of 20 such experiments was a failure, for which no explanation was found. In the remaining 19 experiments in which on 3 occasions the citrate was replaced by the chloride and on 1 other by the sulphate the peak of thrombin generation was delayed by 4–6 minutes. The amount of thrombin produced appeared to be the same as in the controls.

In 3 timed experiments the effect could be demonstrated for up to 6 hours. No positive result was obtained in 3 experiments where peptone alone was taken nor in 2 others with magnesium citrate alone. When magnesium citrate was replaced by sodium citrate in 2 experiments the results were again negative. 30 g. of peptone instead of 50 g. could produce a positive result and 15 g. of glutamic acid (shaken up with 100 ml. water) plus 1 g. Mg^{++} (1 experiment with citrate and 1 with chloride) were equally effective. With 15 g. of glutamic acid, however, the effect lasted 3 hours rather than 6 hours as with 50 g. of peptone.

Prothrombin-time (Quick) and thromboplastin generation



Example of whole-blood thrombin generation after 1 g. Mg^{++} and 50 g. peptone: o—o before mixture was taken, •—• one hour after mixture was taken. After the mixture was taken onset of thrombin generation is delayed by 4 min. The amount of thrombin generated seems to be unaltered.

1. Greville, G. D., Lehmann, H. *J. Physiol.* 1943, **103**, 175.
2. Greville, G. D., Lehmann, H. *Nature, Lond.* 1943, **152**, 81.
3. Schnitzler, B. *Münch. med. Wschr.* 1957, **99**, 81.
4. Malkiel-Shapiró, B., Bersohn, I., Terner, P. E. *Med. Proc.* 1956, **2**, 455.
5. Brown, D. F., McGandy, R. B., Gillie, E., Doyle, J. T. *Lancet*, 1958, ii, 933.
6. Lehmann, H., Pollak, L. *Biochem. J.* 1942, **36**, 672.
7. McCance, R. A., Widdowson, E. M., Lehmann, H. *ibid.* p. 672.
8. Macfarlane, R. G., Biggs, R. *J. clin. Path.* 1953, **6**, 3.

were normal. This was to be expected as both measurements require the addition of Ca^{++}.

An overall shift in the peak of thrombin generation of from 4 to 6 minutes with no individual change being less than 4 minutes is well outside the range of technical error. This confirms earlier and less clear-cut results obtained with the Lee and White method.

A rise in serum-magnesium was not seen regularly 1 hour after the dose, though usually the level rose by 0·2–0·4 mg. per 100 ml. Occasionally a rise as high as 1 mg. per 100 ml. was seen, but abnormally high levels were never encountered. When the dose of magnesium was doubled, and again when one dose was followed 6 hours later by another, no increase in the shift of thrombin generation was obtained and there was no evidence of a cumulative effect. Similarly when a dose was taken on 4 consecutive days but not on the 5th day, a test then performed gave a normal thrombin-generation curve. Indeed if the Mg^{++} effect is due to competition with Ca^{++} an arithmetical increase in this effect would require a logarithmic increase in dosage. We therefore felt confident that, provided renal function was satisfactory, an extension of our observations to patients was justified. 3 patients were treated with magnesium without untoward effects.

A child aged 3 years with sickle-cell anæmia was given 250 mg. Mg^{++} q.d.s. for 4 weeks, but no peptone was given at the same time. There was a rise in the alkali reserve and the urine remained alkaline throughout the 4 weeks. This child usually suffered from some acute pain or other manifestation of sickle-cell crisis every few days, but during the time of treatment remained free from complaint. The hæmoglobin level did not vary. If this observation is significant it might be explained, perhaps, not only by the alkalosis (known to lower the liability of cells to sickle) but also by a prevention of the thrombotic tendency suggested by Ulutin,[9] who noticed hypercoagulability in the blood of patients with sickle-cell anæmia. Such a tendency was also suggested by Walters,[10] who found that children with sickle-cell anæmia showed a greater deposition of fibrin-like material in the liver sinusoids than normal children.

2 patients with ischæmic heart-disease were given 1 g. Mg^{++} and 50 g. peptone t.d.s. There was no effect on myocardial conductivity as shown by the E.C.G. One patient was treated for 2 days, and the alkali reserve rose from 28·4 to 31·0 mEq. per litre, and the other for two weeks with a rise in the alkali reserve to 32·9 mEq. per litre after one week, and to 34·6 mEq. per litre after two weeks. Except in sickle-cell anæmia, when alkalosis might be desirable, we suggest that in any prolonged treatment with magnesium the citrate should be avoided and the chloride or sulphate used instead. As far as patients with cardiovascular disease are concerned it is perhaps of interest that magnesium may affect processes other than coagulation. Selye [11] produced cardiac muscular necrosis and calcification of the aorta in experimental animals by giving steroids, but when magnesium was also given no lesions developed. Extensive cardiovascular calcification has been found in cattle grazing on bauxite soil, which is notoriously deficient in magnesium.[12]

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9. Ulutin, O. N. Personal communication.
10. Walters, J. H. *Proc. R. Soc. Med.* 1958, **51**, 646.
11. Selye, H. Chemical Prevention of Cardiac Necroses. New York, 1958.
12. Arnold, R. M., Fincham, I. H. *J. comp. Path. Ther.* 1950, **60**, 51.

TREBURON AS A BARBITURATE ANTAGONIST?

DURING a study of the pharmacological actions of treburon, which is the sodium salt of sulphated polygalacturonic acid methyl ester methyl glucoside ('Mepesulphate', Roche), we observed that a dog anæsthetised with 30 mg. per kg. of pentobarbitone was aroused to near-consciousness, with increase in the rate and amplitude of respiratory movements, soon after an intravenous injection of treburon. At first we thought this was unrelated to the administration of treburon. But when the same effect was observed repeatedly whereas there was no analeptic action in the unanæsthetised dogs, a causal relationship seemed likely. Consequently we undertook an investigation of the possible antibarbiturate activity of treburon using other animals also.

Treburon is primarily an anticoagulant drug, which was introduced into therapeutics as a substitute for heparin, which it resembles very closely. The available literature does not indicate any associated analeptic action. Convulsions have not been generally noted in acute toxicity studies with treburon, although it has been reported that in mice a dose of 5·5 g. per kg. induced convulsions.[1]

MATERIAL AND METHODS

In our preliminary study the possible antagonistic activity of treburon was tested against pentobarbitone, using 10 adult mongrel dogs, 10 rabbits, and 20 pigeons. Animals of each species were divided into two equal groups. One of the groups served as control, receiving pentobarbitone alone, while the other group had treburon after pentobarbitone was given. The intravenous dose of sodium pentobarbitone was 30 mg. per kg. in dogs and pigeons, and 40 mg. per kg. in rabbits. This dosage, evolved by previous experimentation in a large number of animals, produced a more or less uniform degree of anæsthesia of sufficient duration. Treburon was given when

1. Mangieri, C. N., Engelberg, R., Randall, L. O. *J. Pharmacol.* 1951, **102**, 156.

THE EFFECT OF TREBURON ON THE RIGHTING REFLEXES AND RATE OF RECOVERY AFTER PENTOBARBITONE ANÆSTHESIA

Animals tested	No. in each group	Control group				Group treated with treburon				*t* value	
		Time for return of righting reflexes (min.)		Time for complete recovery (min.)		Time for return of righting reflexes (min.)		Time for complete recovery (min.)		Return of righting reflexes	Complete recovery
		Mean	S.D.	Mean	S.D.	Mean	S.D.	Mean	S.D.		
Dogs	5	222·0	63·6	247·0	66·5	58·4	41·4	98·4	64·6	4·31*	3·16*
Rabbits ..	5	78·4	29·2	104·4	26·3	61·0	31·5	78·2	31·0	1·09	1·29
Pigeons ..	10	101·6	23·8	109·6	26·6	53·2	27·5	63·3	31·2	3·99*	1·12

* Values significant at $P = 0·05$ and at $P = 0·01$. The mean values were subjected to the *t* test.

the animal was completely anæsthetised, which took 5–10 minutes. The dose of treburon was the same as that of sodium pentobarbitone. The antagonistic activity was assessed in terms of the time taken by the animals which had had treburon to show return of the righting reflexes and complete recovery from anæsthesia, as compared with the controls.

RESULTS

The mean and standard deviation of the time taken for return of the righting reflexes and for complete recovery are shown in the table, together with the corresponding *t* values. Statistically the results for the dogs are significant, indicating an appreciable reduction in the duration of anæsthesia after the administration of treburon. For pigeons, only the reduction of time for return of the righting reflexes was statistically significant, and in rabbits neither time was significantly shortened. In the absence of any analeptic effect in unanæsthetised dogs or pigeons, these observations suggest an antagonistic effect of treburon on the short-acting barbiturate pentobarbitone. No toxic effect was noted in the dosage employed.

It is necessary to enlarge the scope of the study by using larger series and also other species of animals, as well as representative long-acting and ultrashort-acting barbiturates, before treburon can be regarded as a general barbiturate antagonist or any speculation on its mode of action can be ventured. We are making studies along these lines.

We wish to thank F. Hoffman la Roche & Co., of Basle, Switzerland, for supplying the 'Mepesulphate', and Mr. D. S. Sevak, M.SC., for assistance with the statistical analysis.

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INTRADERMAL T.A.B.T. VACCINE FOR IMMUNISATION AGAINST ENTERIC

SYSTEMIC and local reactions to inoculation against enteric fever have been a cause of much concern in the Services for many years, and the problem has assumed even greater importance recently because of the possible need to mobilise men, fit for active service, in the shortest possible time.

No change in the frequency or severity of reactions to inoculation was apparent after the adoption of an alcoholised vaccine by the Army and the Royal Air Force in 1943. In 1949 the R.A.F. changed to a combined tetanus and enteric prophylactic containing phenol (T.A.B.T.). At this time the Army was trying to compare the efficacy of alcoholised and phenolised vaccines in the field, but results proved inconclusive and in 1953 they also adopted T.A.B.T. Again no noticeable change occurred in the number and severity of reactions.

For some years it had been reported from the U.S.A., Malaya, and elsewhere that reactions were much reduced when the intradermal route of inoculation was used, though doubt persisted regarding its comparative efficacy especially for *primary* immunisation. This method was, however, adopted by the Army for the *booster* dose of T.A.B. at the time of the Suez crisis in 1956, on the basis of Luippold's observations [1] and studies in the field by Rosenoer [2] and Holt.[3] One report stated that no general reaction was observed following nearly 3800 intradermal inoculations of T.A.B., and local reactions were less than 1%. Using the subcutaneous method, the incidence of general reactions "lay between 5 and 10 per cent" while local reactions "approached 75 per cent".

The introduction of the intradermal route for booster doses of T.A.B. was very favourably received by medical officers and patients, and in 1956 the Director-General Army Medical Services (Lieut.-General Sir Alexander Drummond) invited the Army Pathology Advisory Committee to investigate the possibility of using the intradermal route for primary immunisation with T.A.B.T. The work was placed under the direction of a subcommittee which included representatives of the Royal Navy, the R.A.F., the Wellcome Research Laboratories, and the Lister Institute.[4] This communication summarises the principal findings to date.

TABLE I—DETAILS OF T.A.B.T. VACCINES USED

Volunteer group	Route	T.A.B. component (organisms per ml.)	Tetanus-toxoid component (Lf per ml.)	Dose (ml.)
1	Intradermal	5×10^8	11	0·1 and 0·1
2	Intradermal	5×10^8	22	0·1 and 0·1
3	Intradermal	5×10^8	56	0·1 and 0·1
4	Subcutaneous	$2·5 \times 10^8$	11	0·5 and 0·5
5	Subcutaneous	$2·5 \times 10^8$	11	0·5 and 1·0

The two doses were separated by an interval of five weeks in each case. The T.A.B. component was made up of *S. typhi* 40% (v/v), *S. paratyphi A* and *B* 30% each.

TABLE II—RESPONSE TO THE TETANUS TOXOID COMPONENT FOLLOWING INTRADERMAL AND SUBCUTANEOUS IMMUNISATION WITH T.A.B.T. VACCINES PREPARED FROM VARIOUS CONCENTRATIONS OF CASEIN HYDROLYSATE TETANUS TOXOID

Group	Number of men with tetanus antitoxin (int. u. per ml.)											Geometric means
	>0·02–<0·05	0·05–0·1	0·1–0·2	0·2–0·5	0·5–1	1–2	2–5	5–10	10–20	20–50	Group total	
1	1	..	..	1	3	10	11	3	2	..	31	2·0
2	..	..	..	..	..	7	12	4	2	2	27	3·83
3	..	..	..	..	..	4	13	7	5	1	30	4·75
4	..	..	1	1	1	5	13	8	..	..	29	2·71
5	..	..	..	..	1	4	12	9	4	..	30	4·2

Group 1 received intradermally 0·1, 0·1 ml. T.A.B.T. containing 11 Lf/ml.
" 2 " " " " " " " 22 "
" 3 " " " " " " " 56 "
" 4 " subcutaneously 0·5, 0·5 " " " 11 "
" 5 " " 0·5, 1·0 " " " 11 "
Serum taken two weeks after second inoculation (i.e., bleed II see table III). The two doses were separated by an interval of five weeks in each case.

INVESTIGATIONS

The clinical reactions to intradermal T.A.B.T. were first evaluated under controlled conditions in 162 R.A.F. volunteers, half of whom were given T.A.B.T. subcutaneously and the other half T.A.B.T. intradermally. This trial confirmed the earlier observation that the reaction pattern was milder using the intradermal route.

The antibody and antitoxin responses to T.A.B.T. given by the intradermal and subcutaneous routes using different strengths of tetanus toxoid, and the effects of

1. Luippold, G. F. *Amer. J. publ. Hlth*, 1944, **34**, 1151.
2. Rosenoer, V. M. Confidential Reports to the War Office. 1956.
3. Holt, P. R. *ibid.*
4. The members of the subcommittee are: Colonel M. H. P. SAYERS (chairman), Miss M. BARR, Brigadier L. R. S. MACFARLANE, Prof. A. A. MILES, Dr. H. J. PARISH, Surgeon Rear-Admiral S. G. RAINSFORD, Air Commodore W. P. STAMM, and Major R. P. BRADSHAW (secretary).

giving the antigens separately by various routes and in different sites, have since been studied in over 800 R.A.F. volunteers.

Although serological responses to the T.A.B. components were of the same order using either route, the original preparation of toxoid was not potent enough to give a satisfactory response to the 0·1 ml. dose used in the intradermal method. The most recent trials have been carried out with a toxoid made in casein hydrolysate medium (Mueller and Miller [5]). This toxoid can be readily prepared in high concentration and diluted to any required Lf value. Studies have been made on the responses to the T.A.B. and tetanus toxoid components of the combined prophylactic using varying strengths of the toxoid. The results have shown that, with adequate strength of toxoid, responses of the same order as those following the routine subcutaneous procedure can be achieved with 0·1 ml. doses of the intradermal vaccine. (For details of the vaccines used, see table I.)

Tetanus Toxoid Responses

The responses to the tetanus toxoid components following intradermal and subcutaneous inoculation of T.A.B.T. prepared from the same batch of T.A.B. suspended in different concentrations of toxoid are given in table II.

TABLE III—AGGLUTININ RESPONSES TO THE TO, AO, AND BO ANTIGENS OF POOLED SERA

Reciprocals of highest dilution of serum showing agglutination visible to the naked eye (+ or ±)

Antigen	Pooled sera of group									
	1		2		3		4		5	
	I	II	I	II	I	II	I	II	I	II
AO	0	20	0	20	0	20	0	20	0	20
BO	0	20	0	40	0	20	0	40	0	20
TO	10	40	0	40	0	40	0	40	10	40

I = serum taken before inoculation.
II = serum taken fourteen days after 2nd inoculation.
0 = no agglutination visible to naked eye at dilution of 1 in 10.

The effect of the route of injection can be seen by comparing the responses of the intradermal group 3 and the subcutaneous group 4. The log mean antitoxin response of the intradermal group was significantly higher than that of the subcutaneous group ($t = 2{\cdot}466$, $P = 0{\cdot}01$–$0{\cdot}02$). While there is a suggestion of better responses in the subcutaneous group 5 (11 Lf/ml.) given 0·5 ml. followed by 1·0 ml., they are of the same order as those following intradermal inoculation in group 2 (22 Lf/ml.) and group 3 (56 Lf/ml.).

T.A.B. Responses

For all the intradermal groups the vaccine contained 5000 million organisms per ml. (*Salmonella typhi* 2000, *S. paratyphi-A* 1500, *S. paratyphi-B* 1500 million). The vaccine used for subcutaneous inoculation contained half this number (2500 million organisms per ml. in the same proportions). Thus the intradermal dose of 0·1 ml. was two-fifths of the subcutaneous dose of 0·5 ml. Further details of the dosage, the intervals between injections, and the time of the bleeds (which in the series reported here was chosen primarily for assessing the optimum response to the toxoid) are given in the tables.

The agglutinin responses to the T.O., A.O., and B.O. antigens were approximately the same in all groups and are given in table III. Responses to the Vi antigen were negligible in all cases.

5. Mueller, J. H., Miller, P. A. *J. Bact.* 1954, **67**, 271.

TABLE IV—RESULTS OF A PASSIVE MOUSE PROTECTION TEST AGAINST CHALLENGE WITH *S. paratyphi-B* USING TWO OF THE POOLED SERA FROM VOLUNTEERS IMMUNISED WITH T.A.B.T. VACCINE PREPARED WITH CASEIN HYDROLYSATE TETANUS TOXOID. NUMERATORS: SURVIVORS FIVE DAYS AFTER CHALLENGE. DENOMINATORS: GROUP TOTALS. MOUSE STRAIN: STRONG A MALES

—	Pool 2 (intradermal) Bleed I			Pool 2 (intradermal) Bleed II			Pool 5 (subcutaneous) Bleed II		
Challenge dose	0·25 ml.	0·5 ml.	Total	0·25 ml.	0·5 ml.	Total	0·25 ml.	0·5 ml.	Total
200×10^6	0/10	1/10	1/20	2/10	9/10	11/20	3/10	8/10	11/20

CONTROLS WITH UNIMMUNISED MICE
Groups receiving 200×10^6—0/10.
" " 40×10^6—4/10.
" " 20×10^6—4/10.
" " 10×10^6—4/10.

Immunising dose given by intravenous route. Volume made up to 0·5 ml. with saline for the smaller dose.
Challenge dose given by intraperitoneal route $2^1/_2$ hours after immunisation.
Bleed I: serum taken before inoculation.
Bleed II: serum taken fourteen days after 2nd inoculation.
All challenge doses given in terms of opacity count. (Viable count 36%.)

Pooled sera of volunteers inoculated by the two methods were also compared by a series of passive mouse protection tests.

Bearing in mind the usual limitations of such tests, the results show that there is no significant difference between the degree of protection afforded to mice by the sera (given intravenously) of the subcutaneous and the intradermal groups. The findings of one such test are shown in table IV where the protective effects of the pooled sera from the intradermal group 2 are compared with that of the subcutaneous group 5 against an intraperitoneal challenge of *S. paratyphi-B*.

In both cases significant protection of the same order was conferred.

PRESENT USE

The intradermal method is now being adopted for primary immunisation of the Army in Home Commands. The combined vaccine contains 5000 million organisms per ml. in tetanus toxoid of 20 Lf per ml. All doses are 0·1 ml. The second dose is given four to six weeks after the first and a third dose six to twelve months later. It remains to be seen whether local hypersensitivity develops after intradermal inoculation and whether the effects of a third primary and subsequent booster doses are adequate; but with these caveats the method appears to have distinct advantages over the subcutaneous procedure.

The R.A.F. is for the present continuing to use the subcutaneous method for routine inoculation until there is more evidence on the results of the use of the intradermal route *in the field* as opposed to its use under research conditions, since the skill of the operator may be a factor in deciding the efficacy of the inoculation. In the work reported here, the same operator (Wing-Commander R. M. Cross) has given all the intradermal injections.

The tetanus antitoxin titrations were all performed at The Wellcome Research Laboratories, the T.A.B. studies were carried out at the David Bruce Laboratories, and the inoculations and bleedings were performed by the R.A.F. Institute of Pathology and Tropical Medicine.

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Reviews of Books

The Innervation of Muscle

C. Coërs, chef du département de neurologie de la clinique médicale, Hôpital Brugmann, Brussels University; A. L. Woolf, M.D., consultant pathologist, Midland Centre for Neurosurgery, Smethwick, England. Oxford: Blackwell Scientific Publications. 1959. Pp. 149. 42*s*.

This monograph describes some of the changes seen in intramuscular nerve fibres and endings in a number of neuromuscular diseases. The work was done on biopsy material using mainly intravital methylene-blue for nerve-endings and a modified Koelle's method for cholinesterase. The authors are masters of these techniques and the book is lavishly illustrated with photomicrographs, both plain and coloured, some of which are very beautiful. No other book covers the pathological changes in intramuscular nerves and nerve-endings in a comparable way. It will be of use to the growing numbers who wish to use these techniques to study diseases of muscles and nerves, and they will be particularly grateful for the detailed description of techniques. As yet, however, these methods are essentially for research-workers and not suitable for routine laboratories.

Though many pathological changes in nerve-fibres and endings have been described and illustrated, it is not yet wholly clear how they are related to the various diseases. Much further work remains to be done, but it will be made easier by the pioneer labours recorded here—a happy result of international cooperation.

City Life in Japan

A Study of a Tokyo Ward. R. P. Dore, B.A., associate professor of Asian studies, University of British Columbia. London: Routledge & Kegan Paul. 1958. Pp. 472. 45*s*.

This interesting treatise springs from a six-month inquiry in 1951 into life in a small lower-middle-class district in Tokyo; but it covers much more ground than this localised project would suggest, for it tries to relate the present stage of development in Japan to its history and to other cultures. It is a sociological work, and there are tables, percentages, and appendices; some parts of it are rather long and dull though never obscure. What science takes from the book in readability, however, it amply repays in accuracy and authenticity: the diligent general reader would do better to study far-off lands from carefully constructed works such as these than from the customary novel or travelogue. Reading selectively, the book becomes a fascinating account of how people live and think on the other side of the globe and of the way in which their traditional pattern is breaking up with the impact of changing economic circumstance and Western influence.

The success with which Japan seems to be coping with the legacies of the past twenty years is remarkable, and seems to be deep-rooted. Some Western liberalism has accompanied the mastery of Western technology, and a regime may well emerge which provides an alternative Asian example to China. It is important that we should know about it, and Mr. Dore can certainly help us to understand it. Family relationships, obviously, are closely discussed, and the way they and the social systems around them are changing is the outstanding fact of post-war Japan: the State is being remodelled. The husband-wife partnership is becoming more meaningful, and is taking increasing precedence over blood-ties. Detailed description is also given of education, political attitudes, graft, neighbourliness, community activities, religion, and the individual's changing relationship with society.

The attitude studies are based on tiny samples, however, and conclusions drawn from them may be valid only locally. It must be a matter for regret, too, that a precise account is not given of child-rearing: the cultural approach correlating early formative forces with late results in "national" personality and varieties of mental illness may become a useful method of increasing scientific understanding of the neuroses. There is the odd glimpse of family life—for example, the fact that most families sleep in the same room and that it is usual for children to witness parental intercourse. Some psychoanalysts look gravely upon such experience in infancy, but are their gloomy prognostications justified? This book does not attempt an answer, but it is a matter to which sociologists and anthropologists might turn their attention since the psychoanalysts themselves show little sign of doing so.

The research was done in 1951 and the text apparently written in 1954: surely seven years is too long to elapse between project and public? Nevertheless this is a thoroughly worthwhile account; and we hope that Mr. Dore will spend another six months in Tokyo in 1961 and tell us how everything is working out.

Tumours of the Lungs and Mediastinum

B. M. Fried, M.D., F.C.C.P., assistant attending physician, Montefiore Hospital, New York. London: Henry Kimpton. 1959. Pp. 467. 100*s*.

This much expanded and rewritten version of Dr. Fried's earlier book on the subject is useful, but not without fault. Some sections are full and competent, others are too short or too superficial, so that the balance is unsure. Thus, although there are full descriptions of unusual and rare manifestations and complications of lung cancer, the ætiology of the disease is given very little attention. The important evidence of its association with cigarette smoking occupies only 8½ pages and is not as well documented as the subject deserves. Such a statement as "there is little doubt that the statistical increase in the squamous-cell type of lung cancer . . . is due to improved histological diagnosis and not to the tar contained in cigarettes" surely deserves to be supported by at least one piece of evidence. Throughout the book statistical information seems to be presented with too little regard for such factors as the nature and selection of the material. For instance, the sex-incidence is said to be 82·90% men and 17·10% women, based on 2047 published cases from a variety of hospitals, without taking into account the known variation in the sex ratio with time and place and source of material.

On the other hand, there is much useful clinical description in the various sections on malignant and benign tumours, and though the book lacks the critical precision of a scientific monograph it is a useful manual for the clinician and student.

Obstetric and Gynecologic Milestones

Harold Speert, M.D., assistant professor of clinical obstetrics and gynæcology, Columbia University College of Physicians and Surgeons. New York: The Macmillan Company of New York. 1958. Pp. 700. 105*s*.

Every doctor knows that the language of obstetrics and gynæcology bristles with eponyms: but few may realise that there are at least a hundred in common use. Yet Dr. Speert has listed rather more than that in this book, without recourse to the abstruse or unfamiliar. One consequence of this profusion of names is that, in describing the personality behind each, and reprinting the article that has made it endure, he has written more than a history of his own specialty. This unusual and attractively illustrated book will appeal to many anatomists, general surgeons, and pathologists as well as those to whom it is immediately addressed.

Management of the Newborn (2nd ed. Chicago: Year Book Publishers. London: Interscience Publishers. 1959. Pp. 368. 64*s*.).—This book by Prof. Arthur H. Parmelee, first published in 1952, has been thoroughly revised, for there have been many advances in the past few years. The author has had long experience of the newborn, and the major part of the book is devoted to the physiology and management of the fœtus and the normal newborn infant. Disorders of the newborn are also ably and comprehensively covered. This very practical book is particularly suitable for young pædiatricians, residents, students, and nurses, among whom it has proved very popular, especially in the United States. There is an ample bibliography for more advanced study.

THE LANCET

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Polycythæmia

POLYCYTHÆMIA is one of the less publicised blood diseases, perhaps because it is a chronic and only moderately debilitating disorder, rarely presenting dramatic crises or needing dramatic treatment. Nevertheless it is not uncommon in middle age, and untreated it is potentially dangerous and causes much troublesome depression of health and activity. It is important to recognise the disease early and to distinguish the primary form, in which the bone-marrow is diseased, from the secondary form, in which the polycythæmia is only a symptom. Much can be done today to control primary polycythæmia, to relieve symptoms, and to avert the dangerous complications. Such control can ensure a long and active life-span. Fortunately methods of diagnosis—especially the distinction of polycythæmia vera from secondary forms—have been much improved in the past decade.

Polycythæmia vera is a disorder of bone-marrow nowadays classed as one of the "myeloproliferative" disorders, along with chronic myeloid leukæmia and myelofibrosis; DAMESHEK [1] used this collective term because these three diseases overlap somewhat. The textbooks state that polycythæmia vera starts predominantly in middle life, that males are more commonly affected than females, and that Negroes are rarely and Jews often affected. In 1958 DAMON and HOLUB [2] published their findings in a carefully observed group of patients in New York. Of 197 patients, 132 were men and 65 women. The average age of the group was 53·7 years; but the youngest patient was aged 9 years 9 months, 7 were aged 20–29, 55 were aged 60–69, and 12 were over 70 at the time of diagnosis. Thus, though it is true that middle age is the commonest time for diagnosis, the age-distribution is very wide. Negroes accounted for only 7 of the patients, and this is much less than would be expected from their proportion of the hospital patients generally; on the other hand, Jews totalled 65—about twice as many as would be expected.

The clinical picture of polycythæmia vera in its developed form is easy enough to recognise. The patient has a florid plum-coloured complexion with similarly coloured tongue and mucous membranes. Splenomegaly is always present; sometimes the spleen is only just palpable, sometimes it reaches the iliac crest. The diagnosis is confirmed by the laboratory findings: the red blood-cell count should be over $6^1/_2$ million per c.mm., the hæmoglobin more than 18 g. per 100 ml. (120%), and the hæmatocrit at least 55; leucocytosis (30,000–50,000 per c.mm.) is common, and immature granulocytes are often present (LAWRENCE [3] found them in the blood-films of 111 out of 159 patients); and the platelet-count is often raised—sometimes to a million per c.mm. or more. Sternal bone-marrow smears often show normoblastic hyperplasia, but they give no really diagnostic picture. When some of the signs are missing or equivocal, the diagnosis of primary from secondary polycythæmia may not be easy. The diagnosis is important because there is no point in giving treatment suitable for patients with primary polycythæmia to those who have the secondary form; and if it is established that the polycythæmia is secondary, the cause must be sought. Several differential tests have come into use. Absence of splenomegaly practically rules out primary polycythæmia. PIKE [4] points out that a helpful test is the estimation of arterial oxygen saturation, which distinguishes primary polycythæmia from the secondary form due to hypoxia. A newer test is that for alkaline-phosphatase activity in the polymorph [5]; this gives a strongly positive result in primary polycythæmia, a normal moderate result in secondary polycythæmia, and a negative result in myelogenous leukæmia. Secondary polycythæmia is well known in pulmonary and cardiac conditions that lead to lowered oxygen saturation of the arterial blood, but there are some less known causes. DAMON et al.[6] have lately described 10 cases in which the polycythæmia was associated with renal carcinoma, and they note that there were previous reports of 21 similar cases; only 1 of their 10 patients had a palpably enlarged spleen, and he probably had polycythæmia vera at least four years before the carcinoma appeared. Other tumours that have been accompanied by secondary polycythæmia are cerebellar hæmangioma,[7] uterine fibroids,[2] and very occasionally others. AUERBACH et al.[8] have reminded us of a benign familial polycythæmia in children that gives rise to a picture similar to that of secondary polycythæmia, with a high red-cell count and hæmoglobin level, but normal white-cell and platelet counts and no splenomegaly.

The primary cause of polycythæmia is still unknown. The most widely held view is that the excess of red cells is due to hyperactivity of the bone-marrow, which also accounts for the presence in the blood of increased numbers of polymorphs and platelets. Experimental evidence suggests that the red cells themselves are normal. LONDON et al.,[9] using ^{15}N-labelled glycine, showed that red blood-cells in polycythæmia have a normal life-span and are normally broken up when aged; they calculated that in the case of polycythæmia vera which they studied red cells were being produced at $2^1/_2$ times the normal rate. ELWOOD and DE WARDENER [10] used a differential agglutination technique to follow the survival of red cells taken from patients with polycythæmia vera and transfused into compatible

1. Dameshek, W. *Blood*, 1951, **6**, 372.
2. Damon, A., Holub, D. A. *Ann. intern. Med.* 1958, **49**, 43.
3. Lawrence, J. H. Polycythemia. New York, 1955.
4. Pike, G. M. *New Engl. J. Med.* 1958, **258**, 1250.
5. Leonard, B. J., Israels, M. C. G., Wilkinson, J. F. *Lancet*, 1958, i, 289. Hayhoe, F. G. J., Quaglino, D. *Brit. J. Hæmat.* 1958, **4**, 375.
6. Damon, A., Holub, D. A., Melicow, M. M., Uson, A. F. *Amer. J. Med.* 1958, **25**, 182.
7. Cramer, F., Kimsey, W. *Arch. Neurol. Psychiat.* 1952, **67**, 237.
8. Auerbach, M. L., Wolff, J. A., Mettier, S. R. *Pediatrics*, 1958, **21**, 54.
9. London, I. M., Shemin, D., West, R., Rittenberg, D. *J. biol. Chem.* 1949, **179**, 463.
10. Elwood, J. S., de Wardener, H. E. *J. clin. Path.* 1951, **4**, 218.

normal recipients; in three such experiments the survival of the transfused polycythæmic cells was normal. A rather different result was obtained by BERLIN et al.[11] using ^{14}C for following hæm synthesis; and to explain their results they suggested that there were two red-cell populations, one with a short life-span and the other normal. SHARNEY et al.,[12] using a radioactive-iron tracer, considered that, in accordance with the concept of a "two-pool" system for iron storage and utilisation, red-cell survival was normal. There is, however, general agreement that polycythæmia vera is not due to an unusually long life-span of the red blood-cells.

Experimental work has also been directed to examining the cause of the marrow hyperactivity. Chronic anoxæmia is known to cause polycythæmia—for example, in people who live at very high altitudes. But this sort of polycythæmia differs clinically from polycythæmia vera, and experimentally there is evidence that low oxygen tensions depress marrow activity; for instance, ROSIN and RACHMILEWITZ [13] showed that in bone-marrow cultures reduced oxygen tension caused diminished mitotic activity and increased cell degeneration, whereas high oxygen content increased the activity of the cells. Seeking any humoral cause of primary polycythæmia, CONTOPOULOS et al.[14] made an extract from plasma by a method known to concentrate erythropoietic activity; they used blood from patients with polycythæmia vera and "stress polycythæmia" [15] and from healthy persons. The extracts were injected into rats made anæmic by hypophysectomy. They found that, of 12 rats which received extracts from patients with polycythæmia vera, 9 showed significant increases in red-cell volume and hæmoglobin; plasma from cases of stress polycythæmia and from healthy persons produced no change. Somewhat similar results were obtained by LINMAN and BETHELL.[16] These findings show that the blood of patients with polycythæmia vera contains a factor that stimulates erythropoiesis in rats; but results of this sort have been obtained in other diseases and have not proved to be very significant in the long run. Perhaps this work might be repeated using as the recipients mammals other than rodents.

The treatment of polycythæmia vera has also changed. No-one any longer administers phenylhydrazine or its derivatives; other more easily controlled drugs reduce bone-marrow activity. Radioactive phosphorus (^{32}P) was introduced by LAWRENCE in 1940 and has since been increasingly used. It is given preferably intravenously—sometimes in small divided doses, sometimes in a large single dose. VEREL [17] has published the results of treating 37 patients with ^{32}P in single doses of 7mC; the dose was adjusted according to the estimate of red-cell volume, although he did not find this method of control entirely satisfactory. The treatment reduces the splenomegaly and the leucocytosis as well as the red-cell count and hæmoglobin level. This single-dose treatment gives long periods before further treatment is needed; most of VEREL's patients were given another dose after an interval varying from ten months to over four years. There are, however, some difficulties with ^{32}P treatment. One is that the half-life (14·3 days) is short, and so it is necessary to be reasonably near a source of supply. Then the patients must be admitted to hospital because appreciably radioactive urine is excreted for about four days after the dose. Moreover, some patients prove to be quite resistant to ^{32}P treatment. Since the adoption of treatment with radioactive phosphorus there has been an increased incidence of acute leukæmia in association with polycythæmia vera. PIKE [4] remarks that "whether this relation is one of cause and effect has not been definitely established, but the association is incontrovertible". In practice ^{32}P should not be used for treating the younger patients with an expectation of life of over, say, seven years. Alternatives are repeated venesection and one of the nitrogen-mustard group of drugs. Repeated venesection is useful in relieving symptoms and lessening the risk of complication; but it does not affect the marrow activity, which has to be dealt with as well. The ordinary mustine *B.P.* can be given intravenously in a running drip in doses of 6 mg. at a time. LEONARD et al.[18] obtained good results with triethylene thiophosphoramide, which can be given intramuscularly. This treatment also produces lengthy remissions during which only occasional venesections are required. By one or other of these means patients with polycythæmia vera can be enabled to lead a normal active life; but treatment must be effective and control life-long, because the complications—especially thrombosis—can be dangerous, and in addition the picture may change to one of myelofibrosis or even leukæmia.

Magnesium Depletion

AT the recent conference on electrolytes at the Royal College of Physicians,[19] Dr. PAUL FOURMAN pointed out that the effective treatment of dehydration had allowed patients to survive and later be recognised as suffering from depletion of potassium as well as of sodium. He suggested that the more effective treatment of potassium depletion might similarly pave the way for wider recognition of magnesium depletion. This is a reasonable argument, but the actual search for patients with magnesium depletion has not proved very rewarding numerically, nor has the clinical pattern of magnesium depletion been very firmly drawn. There are a number of possible reasons for this, apart from ignorance of the possibility. For one thing, it is more difficult to induce depletion of magnesium than of potassium: not only do the kidneys effectively conserve magnesium,[20] but there is also a large reservoir of magnesium in the skeleton, which is much less a part of the metabolic pool than, for example, the potassium inside cells. Partly for this

11. Berlin, N. I., Lawrence, J. H., Lee, H. C. *Science*, 1951, **114**, 385.
12. Sharney, L., Schwartz, L., Wasserman, L. R., Port, S., Leavitt, D. *Proc. Soc. exp. Biol., N.Y.* 1954, **87**, 489.
13. Rosin, A., Rachmilewitz, M. *Blood*, 1948, **3**, 165.
14. Contopoulos, A. N., McCombs, R., Lawrence, J. H., Simpson, M. E. *ibid.* 1957, **12**, 614.
15. Lawrence, J. H., Berlin, N. I. *Yale J. Biol. Med.* 1952, **24**, 498.
16. Linman, J. W., Bethell, F. H. *J. Lab. clin. Med.* 1957, **49**, 113.
17. Verel, D. *Quart. J. Med.* 1958, **27**, 27.
18. Leonard, B. J., Israels, M. C. G., Wilkinson, J. F. *Lancet*, 1956, ii, 1017.
19. See *ibid.* March 7, 1959, p. 508.
20. Fitzgerald, M. G., Fourman, P. *Clin. Sci.* 1956, **15**, 635.

reason, any clinical magnesium deficiency would be slow to develop, so that the clinical pattern would be obscured by general malnutrition to a degree which does not have to be reckoned with in the rapidly appearing depletions of sodium and potassium, which are much commoner than the interesting chronic potassium depletion. Even when magnesium depletion is suspected clinically, biochemical support for the diagnosis is much harder to obtain than in the case of sodium or potassium. Flame photometry for magnesium is possible but technically more difficult than for sodium and potassium, and the colorimetric methods are of low specificity. Because of the large output of magnesium in the fæces, as with calcium, balance studies which do not include the stools are of no value: this raises the problems of marking and of long collection periods, which can at a first approximation be neglected in the study of sodium, and to some extent of potassium, where the fæcal component of excretion is normally very small. Isotope-dilution methods, which are now contributing regularly to our assessment of sodium and potassium depletion, are much less convenient with magnesium, whose available isotopes are less accommodating than ^{42}K or ^{24}Na.

These difficulties are challenging, but by no means insuperable, so long as they are not accepted as an excuse for inactivity. While it would be quite misleading to say that magnesium depletion has established itself as either a frequent or a well-recognised syndrome comparable to potassium depletion, steady progress is nevertheless being made in the development of suitable technical methods and in their clinical application. Experimental studies of magnesium depletion in man have been too limited to shed much light on the clinical symptoms which might be expected; but experimental depletion in animals is beginning to yield interesting biochemical results [21] which may some day find a place in our understanding of the clinical syndrome. Using a much improved method of flame photometry for magnesium, these inquiries have confirmed an association of magnesium depletion with hypercalcæmia and calcification of the kidneys, first observed many years ago.[22] Another interesting finding was that although the diet given to produce magnesium depletion was adequate in its content of potassium, analysis of muscle nevertheless showed a fall in potassium content which was closely correlated with the fall in magnesium content: a suggested explanation is that magnesium depletion impairs the function of the mitochondria, which are known to be important in the intracellular accumulation of potassium.[23] Other work has shown that on a magnesium-deficient diet muscle potassium was definitely reduced even when the decrease in magnesium itself was "minimal" [24]; and there was no increase in cellular sodium or in serum-bicarbonate such as occurs when potassium depletion is the primary abnormality.[25] Even the limited degree of magnesium depletion which has been induced in man was associated with some loss of potassium from the body.[19] Vasodilatation was conspicuous in the magnesium-depleted rats, as in the classical studies of McCollum.[26]

A new approach in the study of magnesium has been provided by the isotope ^{28}Mg, which has a half-life of 21 hours. Distribution studies have indicated that the early "magnesium-space" is greater than the magnesium in extracellular fluid, but substantially less than the total body content.[27] The clinical application of this isotope has been limited by difficulty in producing it, and by the low specific activity of available material; but these difficulties will no doubt be overcome.

Experimental findings are now being complemented by an increasing number of case-reports in which the rather inadequate evidence of a low serum-magnesium is supported by the demonstration either of abnormal magnesium losses or of retention of magnesium during recovery. Card and Marks [28] have described a patient with an ileal fistula in whom the magnesium deficit was of the order of 350 mEq. out of a calculated initial magnesium content in the body of 1180 mEq. As the magnesium depletion increased, the patient became excitable and apprehensive, and needed much larger doses of sedatives. There was no tetany, and the electrocardiogram was within normal limits. When magnesium was given, she retained 279 mEq. over a 3-week period; but clinical improvement occurred within 48 hours of starting intravenous magnesium sulphate, during which time the excitement disappeared, and normal doses of sedatives were again effective. Randall et al.[29] describe 12 patients with "psychiatric and neuromuscular symptoms", which were attributed to magnesium deficiency largely on circumstantial evidence; but in 6 of them retention of between 40% and 90% of administered magnesium was demonstrated, concurrently with remission of symptoms, which in some of the patients was rapid and dramatic. The psychiatric symptoms included confusion and disorientation, and 7 patients became delirious. Muscle twitching was present in all the patients, and tremor in half; myoclonus, athetoid movements, and fasciculation were also observed, but tetany was seen in only 1. In 2 patients, calcium given without magnesium failed to abate the symptoms.

There are some interesting discrepancies between experimental magnesium depletion in the rat, and the clinical picture which emerges from these recent reports. Whereas hypercalcæmia is found in the rat, the serum-calcium in Card's [28] patient was 8·1 mg., while in the Boston series [29] "hypocalcæmia of a moderate to a marked degree was present in all 12 patients". It seems likely that in the patients the circumstances causing loss of magnesium also led to loss of calcium from the body, whereas in the animal work the calcium intake was carefully maintained. Two findings which are common in

21. MacIntyre, I., Davidson, D. *Biochem. J.* 1958, **69**, 6P.
22. Greenberg, D. M., Lucia, S. P., Tufts, E. V. *Amer. J. Physiol.* 1938, **121**, 424.
23. Stanbury, S. W., Mudge, G. H. *Proc. Soc. exp. Biol., N.Y.* 1953, **82**, 675.
24. Cotlove, E., Holliday, M. A., Schwartz, R., Wallace, W. M. *Amer. J. Physiol.* 1951, **167**, 665.
25. Darrow, D. C., Schwartz, R., Iannucci, J. F., Coville, F. *J. clin. Invest*, 1948, **27**, 198.
26. Kruse, H. D., Orent, E. R., McCollum, E. V. *J. biol. Chem.* 1932, **96**, 519.
27. Glicksman, A. S., Schwartz, M. K., Bane, H., Roberts, K. E., Randall, H. T. *Clin. Res. Proc.* 1956, **4**, 14.
28. Card, W. I., Marks, I. N. Ciba Foundation Colloquia on Ageing, 1958, **4**, 301.
29. Randall, R. E., Rossmeisl, E. C., Bleifer, K. H. *Ann. intern. Med.* 1959, **50**, 257.

the animal work, but apparently rare in clinical magnesium depletion, are tetany and vasodilatation; the absence of tetany is the more surprising in view of serum-calcium values as low as 6 mg. per 100 ml. Further experiment and experience will be needed to explain these apparent anomalies, and to sharpen our critique of clinical magnesium depletion. And the effect of magnesium on blood coagulation, the subject of the preliminary communication by Dr. ANSTALL and his colleagues on p. 814, is another aspect of the matter that is full of interest.

Surface-area, Weight, and Water

FOR some time it has been quite widely accepted that the surface-area of the body, metabolic rate, and daily water requirements are interrelated; but last year the use of this supposed relationship as a basis for calculating amounts of fluid to be administered parenterally was challenged by OLIVER et al.[1] For clinical purposes surface-area is usually calculated from standard charts [2] or from nomograms.[3] OLIVER et al.[1] have drawn attention to the small number of direct measurements of surface-area on which the 37 formulas for calculation are based; and they remind us that all the nomograms in common use are derived from the original equations of DU BOIS and DU BOIS, which were based on measurements of only 12 patients, of whom only 4 were healthy and only 1 (a rickety child) less than 12 years of age. BOYD [4] plotted all the recorded measurements of surface-area against the surface-area of the same subjects as predicted by the equations of DU BOIS and DU BOIS, and found that the standard deviation was 7·5% for those weighing more than 3 kg. and 18·6% for infants weighing less than 3 kg. BOYD was able to derive a formula which gave a standard deviation of 7·1% for all ages and weights; and she noticed that when height was ignored the deviation was only 0·7% greater. OLIVER et al. suggest that this small difference does not justify the belief that surface-area is a better unit of physiological function than weight alone.

BENEDICT and TALBOT [5] used the linear formula of DU BOIS and DU BOIS to calculate the surface-area of normal infants and children and also measured basal metabolic rate. When for comparison the individual heat productions were corrected to a surface-area of 1 sq. m. it was evident that heat production did not conform at all to the conventional 1000 calories per sq. m. Instead there was a progressive increase in heat production up to about 1150 calories for a body-surface area of 0·5–0·6 sq. m. and then a gradual decrease in the larger subjects to about 1000 calories at 1·0 sq. m. Thus heat production is not related closely to either surface-area or body-weight. Although it was RUBNER who, in 1883, originally suggested that in warm-blooded animals such as dogs the daily heat production was 1000 calories per sq. m., it should be remembered that he subsequently reduced this estimate to about 615 calories at an environmental temperature of 30°C.[6] OLIVER et al. are justified in reminding us of BENEDICT's conclusion that emphasis should be placed on "non-uniformity in heat production" rather than on "uniformity in heat loss".

Various physiological functions have been related to the calculated surface-area, but there seems to be growing dissatisfaction with this convention and a tendency to express these functions in terms of organ-weight or total body-weight. Average organ-weight is unlikely to be any more satisfactory a standard, even for the healthy person, than calculated surface-area. Actual body-weight also depends so much on the fat content, and coexisting or earlier disease, that it may differ greatly from the average weight range even when allowance is made for sex and age; moreover the so-called standard weight tables range broadly at each age and do not always state whether any or how much allowance should be made for clothing. The proportion of the total body-weight which is important in assessing physiological functions is the weight of the lean tissue mass, in which the acute metabolic activity of the body is situated, and this can be derived by subtracting the weight of storage fat from total body-weight. Fat content can be estimated in various ways; but the simplest—by calculation from the specific gravity measured by weighing the body in air and when totally immersed in water—is seldom practised even in physiological laboratories and is hardly suitable for general clinical use.

The chief advantage of using body-weight as a basis for calculation of the theoretical daily energy and water requirements lies in the ease and accuracy with which the body can be weighed; a 1 oz. error in weighing a 10 lb. baby amounts to only 0·6%. The daily quantity of water orthodoxly allowed to such a child is 60 ± 15 ml. per lb. weight—a range of 450–750 ml.—and this rate of allowance is applied from weights of 5 to 22 lb. (2 to 10 kg.).[1] When larger children are concerned the daily range increases from 1155–2145 ml. (50 ± 15 ml. per lb.) at 33 lb. (15 kg.) to 2200–5500 (35 ± 15 ml. per lb.) at 110 lb. (50 kg.). When these daily water allotments for bodies weighing 11 lb. and 110 lb. are compared by referring both to the standard of an "ideal" 42 litres of body-water, the ration of a 110 lb. child is only two-thirds that of the 11 lb. child. This conforms well with the period of greatest metabolic activity in childhood between the ages of 6 and 24 months or weights of about 11–33 lb. (5 to 15 kg).[8] The calculation of water intake in this way appears to work satisfactorily for infants and when the water is taken by mouth as milk and in, or accompanied by, other food. In older children who have no serious disturbance of normal function the volumes seem to be too large for safe parenteral administration.

OLIVER et al. rightly emphasise that such sets of rules for the parenteral administration of fluids to sick

1. Oliver, W. J., Graham, B. D., Wilson, J. L. *J. Amer. med. Ass.* 1958, **167**, 1211.
2. Du Bois, D., Du Bois, E. F. *Arch. intern. Med.* 1916, **17**, 863.
3. Boothby, W. M., Sandiford, R. B. *Boston med. Surg. J.* 1921, **185**, 337.
4. Boyd, E. Growth of Surface Area of Human Body. Minneapolis, 1935.
5. Benedict, F. G., Talbot, F. B. Metabolism and Growth from Birth to Puberty. Washington, 1921.
6. Rubner, M. *S.B. preuss. Akad. Wiss.* 1931, phys. math. Kl. nos. 16-18, p. 272.
7. Benedict, F. G. Vital Energetics: Study in Comparative Basal Metabolism; p. 194. Washington, 1938.
8. Holliday, M. A., Segar, W. E. *Pediatrics*, 1957, **19**, 823.

babies can never be a substitute for clinical judgment, and that the riper the judgment the less the rules are needed or heeded. Unfortunately such rules, with their wide ranges of so-called tolerance, are potentially most dangerous when used by those clinicians whose lack of previous experience they are designed to make good.

Annotations

INFECTION OF PETS

ABOUT the middle of the late war it was found that many cases of food-poisoning, caused by species of salmonella not seen hitherto in England, were derived from dried eggs imported from the U.S.A.[1] Man was not the only sufferer, because some of these eggs, condemned as unfit for human food, were fed to pigs. Whether man was also infected by eating bacon or sausages is uncertain. More recently there have been large imports of egg in various forms from China, and some batches of these have been shown to be even richer in salmonellæ.[2] By cooperation between the two ends this danger has been reduced, but a letter in the *Veterinary Record* reports that egg of Chinese origin was responsible for a severe attack of the merry-go-whimbles in an African grey parrot.[3] The source of the infection is described as " dried egg yolk ", which seems to have been included in a ready-prepared seed mixture.

The difference between affluence and Carey Street in the food trade is said to rest on the profitable use of every part of the raw product, and for this reason it is common practice to use for animal food all that cannot be wished on the guileless public. Hence the regulations—subject to some rather unreasonable criticism in Parliament—which compel those who sell meat unfit for human consumption as food for pets to cook it and stain it with an indelible dye. Indeed, the more we know the more dangerous does the keeping of pets seem. They claw and bite us, and by so doing infect us with organisms such as *Hæmophilus bronchisepticus* and the unidentified agent which causes " cat-scratch fever ". They give us psittacosis, and if we are very unlucky an infection with *Leptospira canicola*. Cats and dogs suffer from tuberculosis, and, though human infection from this source has not been proved beyond all doubt, the association of tuberculosis in the pet and its master is fairly common. Almost every kind of animal and bird can be infected with salmonellæ, and most of the species from these sources can cause disease in man. Considering the intimacy allowed to their pets by many families, it is surprising that infections are not more frequent. Those who let the dog sleep on the bed or get the cat to lick the plates are asking for trouble.

NUCLEOHISTONE AND THE L.E. FACTOR

THE sera of most patients with disseminated lupus erythematosus (D.L.E.) react with cell nuclei or with some material extractable from them. In the original observation of Hargraves et al.[4] this feature was revealed by the appearance in marrow smears of patients with D.L.E. of polymorphs with a characteristic cytoplasmic inclusion, now known to be the phagocyted and altered nucleus of another polymorph. Later work has established that this appearance is due to a property of the serum which induces the effect also in cells of other individuals and, indeed, of other species. In addition to this ability to induce the appearance of these so-called L.E. cells, the sera of many of these patients give both a precipitin reaction and complement fixation with desoxyribonucleic acid (D.N.A.). The affinity of the serum factor for cell nuclei in general has been demonstrated by means of a fluorescent antibody to human γ-globulin.[5,6] For this purpose a fresh-frozen section is first treated with the test serum, and fixation of γ-globulin to the nuclei is detected by staining with a fluorescent rabbit anti-human γ-globulin.

The serum of patients with D.L.E. has been intensively investigated in an effort to detect the factor or factors responsible for these reactions. The factor responsible for precipitation with D.N.A., which behaves in many ways as an antibody, is not responsible for the positive L.E.-cell test or for the nuclear affinity revealed by the fluorescent-antibody method, since these last two properties are retained after the addition of an excess of D.N.A.[7] But whole nuclei or D.N.A. protein remove all these three properties [8]; from which it must be inferred that L.E.-cell formation and nuclear affinity are due to a factor or factors directed, not against D.N.A., but against its protein complex with histone in the somatic nuclei. The necessity for the presence of histone as well as D.N.A., at least for the nuclear affinity test, has been shown for artificial D.N.A.-protein complexes by Friou [9]; and this finding is strongly supported by two short papers which we publish this week.

It has long been known that two distinct types of basic proteins are combined with the D.N.A. in cell nuclei. In the nuclei of somatic cells the basic protein is invariably a histone, while in the nuclear material of the sperm heads of most animals the corresponding protein is a protamine. If, therefore, histone is an essential component of the nuclear material that reacts with the serum factor in the " nuclear affinity " test, then this test should prove negative with spermatozoa in which the protein is a protamine. This is precisely the result reported and illustrated by Dr. Holborow and Dr. Weir (p. 809). On the other hand, it seems from Dr. Baum's paper (p. 810) that a specific antigen is present in the sperm heads of guineapigs, since he showed by the same fluorescent-antibody method that the serum of guineapigs immunised with guineapig testis in Freund's adjuvant reacts in vitro with the heads of the spermatozoa of the same species but not with other nuclear material. It has yet to be proved that this " autoantibody " in guineapigs is directed against the nucleoprotein of the sperm head, as seems probable. The work of Holborow and Weir on the one hand and of Baum on the other strongly suggests, therefore, that the immunological specificity of a D.N.A. protein is determined, not by the D.N.A., which is presumably the same in both the somatic cells and sperm heads of a single individual, but by the basic protein with which it is combined; and further that in D.L.E. the factor responsible for nuclear affinity is directed against nucleohistone and not against nucleoprotamine. Finally, since histone alone is apparently incapable of reacting specifically with this factor,

1. *Spec. Rep. Ser. med. Res. Coun., Lond.* 1947, *no.* 260.
2. Smith, M. E., Hobb, B. C. *Mon. Bull. Minist. Hlth Lab. Serv.* 1955, **14**, 154.
3. Graham-Jones, O., Fiennes, R. N. *Vet. Rec.* 1959, **71**, 245.
4. Hargraves, M. M., Richmond, H., Morton R. *Proc. Mayo Clin.* 1948, **23**, 25.
5. Holborow, E. J., Weir, D. M., Johnson, G. D. *Brit. med. J.* 1957, ii, 732.
6. Friou, G. J., Finch, S. C., Detre, K. D. *J. Immunol.* 1958, **80**, 324.
7. Deicher, H. R., Holman, H. R., Kunkel, H. G. *J. exp. Med.* 1959, **109**, 97.
8. Holman, H. R., Kunkel, H. G. *Science*, 1957, **126**, 162.
9. Friou, G. J. *J. Immunol.* 1958, **80**, 476.

the specificity must reside in the shape of the D.N.A.-histone complex—a shape which, we must conclude, is distinct from that of either of its two separate components.

WILMS' TUMOUR

WE are pleased if we can recollect that Wilms' tumour is a rare tumour of the kidney found in children: we may even remember that its modern name is nephroblastoma [1] and, because it is derived from the immature renal blastema, it may contain not only epithelial elements of tubules and incompletely formed glomeruli as well as connective tissue or sarcomatous elements, but also striated muscle, cartilage, or even bone. Our pleasure is clouded by the belief that such a tumour is very commonly fatal, only a few fortunate patients being saved by operation.

The two-year-survival rate of patients with Wilms' tumour before 1934 was only 9% [2]; but Lattimer et al.[2] bring the welcome news that, of their 42 cases treated since then, 16 survived for two or more years after operation. In their series females were slightly preponderant (in most series [1] males are about twice as numerous as females); the tumours were equally frequent on each side, and in 4 patients there were bilateral growths. Tumours at the lower pole carried a better prognosis, being more easily palpable and surrounded by loose fatty coverings which could absorb some local extension and still be removed successfully with the tumour. The most important finding was that the age of onset was closely linked with the two-year-survival rate; this was 90% in children whose tumours were treated before the age of 1 year, 70% at 0–2 years, but only 18% above that age. The majority of the tumours were in children under 5 years. These figures provide a powerful argument for careful abdominal palpation of all infants not only at birth but also at intervals in the first 2 years, and for immediate investigation and treatment of any intra-abdominal mass or unexplained hæmaturia. This tumour apparently runs contrary to the general experience of tumours—the younger the patient the greater the malignancy.

All the patients had a palpable abdominal mass, and 60% had hypertension which was cured by removing the tumour; a high proportion had either gross hæmaturia or red blood-cells in the urine. As regards differential diagnosis, sympathicoblastoma often simulated Wilms' tumour: but sympathicoblastoma displaced or distorted the kidney in such a way that it could be distinguished by retrograde pyelography; it gave rise to metastases in bones; or it extended across the midline and became nodular and fixed, whereas the Wilms' tumours were confined to one side and remained globular and somewhat mobile. Hydronephrosis was the commonest single cause of palpable abdominal masses, and this lesion was diagnosed by transillumination in a dark room or by retrograde pyelography. Cystic disease of the kidneys was also fairly common. The frequency of these simple lesions was the chief reason for not giving preoperative radiotherapy.

The standard treatment was nephrectomy followed by radiation, though a few patients who underwent nephrectomy alone also did very well. The great majority of the patients who died postoperatively did so within the first 2 years, and after that time the chance of cure was good. Radiotherapy may cause the disappearance of occasional lung metastases, but Lattimer et al. warn against the ill effects; radiotherapy stunted bone growth on one side in several children and caused complete atrophy of an ovary in 1. The radiosensitivity of Wilms' tumours differs widely, and is quite unpredictable even after histological study. The value of radiotherapy is probably more precautionary than curative, and Lattimer's good results should be ascribed mainly to prompt diagnosis and operation. Therein lies our cue.

1. Willis, R. A. Pathology of Tumours; p. 925. London, 1948.
2. Lattimer, J. K., Melicow, M. M., Uson, A. C. *N.Y. St. J. Med.* 1959, **59**, 415.

FITTING THE JOB TO THE WORKER

THE idea that the job can be fitted to the worker has gradually gained strength from the early days when balloonists died from lack of oxygen and coalminers were killed by gross environmental abnormalities. The physiologists were first in this field, under the leadership of such eminent men as J. S. Haldane, studying such problems as the decompression of divers and the composition of coalmine atmospheres.

In the first week of March this year an international (although mostly Western European) conference was held in Zürich on the subject of fitting the job to the worker. It aimed at presenting to representatives of both employers and workers the methods and results of applying the biological sciences to this general task.

Heavy muscular work, the anatomical factors in work design, the presentation and use of information, the shaping and layout of controls, the lighting, noise, and climate of the workplace and its arrangement, were all discussed. It was hoped by the European Productivity Agency of the Organisation for European Economic Cooperation, which convened the conference, that in this way industry could be made aware of the resources which can be put at its disposal for improving workplaces. The United Kingdom sent a strong delegation, most of them members of the Ergonomics Research Society. Anatomists from Oxford, very much interested in the live body, joined with physiologists from London and the Medical Research Council's staff concerned with the practical control of the environment and with equipment design. The Universities of Cambridge and Reading, together with the British boot and shoe industry, contributed the applied psychologists, and the University of Durham sent the medical head of its department of industrial health in Newcastle. There were similar, but rather smaller, delegations from Scandinavia, Western Germany, Holland, Belgium, France, Switzerland, and Italy.

Thus the pattern changes. The human biologist is now right outside his laboratory, suggesting to both sides of industry how the environment might be improved. Industry, however, is managed by engineers, chemists, lawyers, and accountants, with physicists quickly coming up, and none of them has had a training in the human limitations of the environment which they control. Doctors are the only sizable group employed in factories who come near to understanding this; but even they may be restricted by their own or their management's conception of their role, or by the load of purely clinical work.

The Ergonomics Research Society has returned this month to Oxford, the place of its birth, to celebrate its tenth anniversary, and to review the past and gaze into the future. Notwithstanding its queer title, this society has flourished, and it now has an international reputation. The time may be approaching for it to consider bringing its subject to the notice of three groups of people in authority in British industry—doctors, management and men, and those in charge of technical education. Perhaps a series of small, separate conferences, on the Zürich model, for each of these groups, with carefully selected participants, should be arranged. Such meetings can only do good in so far as they bring together the points of view of human biologist, industrial manager, and technical teacher.

Special Articles

MEDICAL CARE OF THE ADOLESCENT

Report from the British Pædiatric Association*

WE have not attempted to lay down an age-limit for adolescence; we define it as the phase of intellectual, social, emotional, and physical change through which the individual progresses in passing from childhood to maturity. It comprises, then, not only children in their final school years, but also young workers in their early years of employment. Although we were naturally concerned with the place of the pædiatrician in the medical care of the adolescent, the object of our inquiry was to determine whether the medical services which were now provided for the adolescent were adequate, and whether further provision was necessary and in what direction. We deprecate any further division of medicine by age-groups, and we do not take the view that the responsibility for the health of the adolescent should be the pædiatricians' alone: we agree that family doctors, psychiatrists, general physicians, other medical specialists, and the School Health Service can have an equal interest in this age-group. We hope our recommendations may lead to closer collaboration between these different specialists. While it seems right to us that the pædiatrician may wish to care for patients during puberty and after, we recognise that general physicians and other specialists may have a particular interest in some aspects of disease in childhood and adolescence. Though medicine has, for good and sufficient reasons, become divided, Man is indivisible. The care of the adolescent should provide a common meeting-place for doctors with different interests.

There are no special physical problems in this age-group other than those associated with puberty; but there are important psychological situations emerging at this time which may involve not only all these medical agencies but also to a wide degree the social services. In so far as physical disorders are concerned, several recent surveys [1 2] have shown that this is an age-group in which there may be a failure of medical care—in prevention, in diagnosis, and in treatment—and this emphasises both the importance of the continuing care of the family doctor and the responsibility falling on the school and factory health services. All the other agencies which look after the adolescent in hospital, in school, and in industry have a special duty to keep the family doctor informed about his patients. He alone can coordinate their activities to the advantage of his patient, and, when all these other agencies have completed their work, he will remain the patient's medical adviser.

Our recommendations may appear to some to duplicate unnecessarily the services devoted to the medical care of the adolescent. We cheerfully rebut this criticism. We see no danger in this multiplicity of care, but only increased safety for the adolescent, providing there is a close liaison between all the interested parties. To illustrate this point we may describe a common situation:

The family doctor discovers an organic systolic murmur in a schoolchild; the exact diagnosis of congenital heart-disease requires reference to a pædiatrician and, possibly, to a cardiologist; the school medical officer will supervise the child's activities in school; the family doctor will treat the child's intermittent infections; the dental surgeon and the laryngologist must be made aware that any operation requires penicillin cover; the parents must be told of all the associated hazards; the pædiatrician is responsible, when the time comes, for ensuring that continuing care is provided by a general physician or cardiologist.

This chain is long and complicated; and its strength depends on close linkage.

INPATIENT ACCOMMODATION FOR ADOLESCENTS

In many hospitals adolescents are admitted to adult wards; in others, both in general and children's hospitals, they are accommodated in single or two-bedded wards; in some children's hospitals adolescents are admitted, unless there is some specific reason for not doing so, into wards with younger children. We think there are good reasons for preferring not to admit adolescents either into adult wards or into wards with young children; though we admit that some adolescents will not be harmed by this practice.

We think that more children's hospitals and children's departments should take the opportunity of opening small adolescent wards where male and female adolescents can be accommodated separately. Such an experiment has been conducted for several years at the City General Hospital, Sheffield (Dr. R. R. Gordon); and we have been impressed by the happiness and wellbeing of these children, and by the absence of any special problems for the nursing staff in the management of these wards.

Even where these adolescents' beds are under the general care of the pædiatrician, other interested consultants should be invited to have charge of patients in these beds. It is unnecessary to add that there must be the fullest cooperation between members of the consultant staff in the management of these wards. In general hospitals, adolescent wards in the children's department should provide a useful opportunity for collaboration, not only between pædiatricians and general physicians but also with other specialists such as psychiatrists and gynæcologists.

As far as we can tell, 10–20 adolescents' beds would be an adequate provision for a total population of 500,000 persons. The Nuffield Foundation (division for architectural studies; Mr. R. Llewelyn Davies) has conducted an inquiry with regard to the numbers of children, both young (1–11+ years) and adolescent (12–16+ years), admitted to adult wards. The numbers in each group are nearly identical and each contains about one-fifth of the total number of children admitted to children's wards in the same hospital areas in the same period.

Although the number of children and adolescents admitted to adult wards is approximately the same, yet their distribution among the different specialties is very different. While 80% of the young children are in ear-nose-and-throat and general surgical wards, only 60% of the adolescents are to be found in these wards and 25% of them are in medical and orthopædic wards.

OUTPATIENT ADOLESCENT CLINICS

We considered carefully the adolescent unit in the Children's Medical Center in Boston. We agreed that there would be no place in our medical services for an experiment of this kind. We should, however, like to

* From an interim report by a committee set up by the British Pædiatric Association. The members are Dr. RONALD GORDON, Prof. DOUGLAS HUBBLE (convener and secretary), Dr. RONALD MAC KEITH, Dr. VICTORIA SMALLPEICE, and Dr. R. E. SMITH.

1. Herford, M. E. M. Youth at Work: a five-year study by an appointed factory doctor. London, 1957.
2. Lee, J. A. H. *Brit. med. J.* 1958, i, 573.

know whether there is a demand by family doctors and by parents for special outpatient clinics for adolescents; we assume that such clinics would be concerned with some physical disorders (for example, those connected with puberty) but would be largely occupied with psychological disorders and with problems of behaviour. We hope that a few such clinics will be initiated, whether by pædiatricians or by general physicians, in order that the need for them may be better judged.

THE SCHOOL HEALTH SERVICE

There has been much discussion in recent years concerning the School Health Service and its reform.

We shall not discuss in detail any of the changes which have been proposed. We should, however, like to see both the family doctor and the pædiatrician more actively concerned in the service. Already a large number of general practitioners are working in the service, and in Oxfordshire nearly all the periodical school medical examinations are conducted by general practitioners. We believe that there is now in this country a large body of young, active, and instructed general practitioners who would do this work well and who would strengthen the diagnostic side of the service. These doctors have too a greater knowledge of therapeutic possibilities than do many school medical officers.

We believe that the pædiatrician should be increasingly employed in the ascertainment and care of handicapped children. Since the war, a generation of pædiatricians has emerged with a special knowledge of the problems of the handicapped child, and fuller use of these experts should be made, especially in the day and residential schools for mentally and physically handicapped children.

PSYCHOLOGICAL DISORDERS

Many of the problems for which adolescents consult doctors are psychological. Adolescents are in process of adjustment to rapid growth and to changes in endocrine balance; they are proceeding, at a different rate and with varying degrees of stability, to sexual, emotional, and intellectual maturity. Sometimes unresolved conflicts from earlier ages become prominent again. Adolescents may have good support in their homes; but not all parents have an adequate understanding of their behaviour problems. Again, adolescents are often disposed to look outside the family for guidance.

There are many minor and major problems, for which help is asked.

A major problem is juvenile delinquency. Delinquency is largely a disorder of adolescence from which many recover permanently and since the prognosis is potentially good, the management and treatment of the offender are important.

Psychosis may appear at adolescence. Its early recognition is essential, and there is a special opportunity in this age-group for research to determine the origins of psychosis in the interplay of constitution and environment.

A third major problem is the care of the handicapped adolescent, and here pædiatricians can make a large contribution. These young people stay longer at school and in many ways the psychological problems of adolescence press more hardly upon them. Pædiatricians with special experience of both the physical problem and its psychological consequences are well equipped to give help to the handicapped adolescent.

Many psychological problems of adolescents are solved within their families or by persons other than doctors—schoolmasters, ministers, wise friends. Some are dealt with by family doctors. Some are referred to consultant pædiatricians or to general physicians. Interested pædiatricians can develop methods of dealing with these problems through their personal experience, and they can learn much by cooperation with the psychiatrists.

Sometimes the pædiatrician or the children's psychiatrist will wish to admit these young people to hospital for observation and investigation. This admission may be to pædiatric beds, but prolonged inpatient treatment of psychological disorders will usually require expert psychiatric supervision. The provision of more inpatient psychiatric units for the treatment of, and research into, the major psychological disorders of adolescents is urgently needed. In their capacity as advisers on the welfare of young people, pædiatricians in every region should urge that such accommodation, which is now generally lacking, should be quickly provided.

We are grateful for help from the senior administrative medical officers of the regional hospital boards, of the Nuffield Foundation (division for architectural studies), Mr. R. Llewelyn Davies and Dr. Barbara Duncum, Dr. George Davison (Newcastle), Prof. R. W. B. Ellis (Edinburgh), Dr. J. Roswell Gallagher (Children's Medical Center, Boston, Mass.), Dr. G. H. Gibson (M.O.H. for Leicestershire), Dr. Cedric Harvey (Doncaster), Dr. Peter Henderson (Ministry of Education), Dr. M. E. M. Herford (Slough Industrial Centre), Dr. J. D. Kershaw (M.O.H. for Colchester), Dr. J. A. H. Lee (Medical Research Council), Dr. G. D. Pirrie (London County Council), and Dr. Marion Taylor (School Health Service, Sheffield).

IDENTIFICATION FOR THE DISABLED ON PUBLIC TRANSPORT

J. M. M. McKENZIE
M.B. W'srand
From the Astley Ainslie Hospital, Edinburgh, 9

AN important part of rehabilitation is to help disabled patients to become as mobile as possible—first in the hospital, later in the home, and finally in travelling on public transport. But those who are permanently disabled may never become agile or quick, and some of them may have very real difficulty in boarding a bus, getting to and from a seat, and alighting. They rightly fear that they may not be given enough time.

It was felt that some means of identification might help to overcome these difficulties, especially for those patients whose disability is not obvious. Bus drivers and conductors are, on the whole, sympathetic to people obviously disabled—notably the blind, who are easily recognised by the white stick. We thought that if those with other disabilities were provided with a suitable token to mark their disablement, they too would receive that little extra help and time they need.

It was finally decided that the means of identification should be a small bright disc, mounted on elastic, and worn inside the wrist. This would normally be covered by the sleeve but could easily be shown, and yet leave both hands free.

After trial and error, the disc, as shown in the figure was devised. It is $1\frac{1}{2}$ in. square and is made of clear 'Perspex' painted on the wrist side with special fluorescent paint. A T of luminous tape, as used for motor-car bumpers, is superimposed on the front surface (the T is for transport). The

discs were made in the outpatient occupational-therapy department, at a cost of about 4½*d.* each.

The manager of the Edinburgh Corporation Transport Department cooperated readily in the initial experiment. The idea was not to force the bus operatives to be kind, but simply to indicate those who needed their consideration. The scheme was welcomed also as a method of preventing accidents.

All the depots in the area were circularised with the necessary information, and a pilot trial for 18 patients was run for four weeks. The high proportion of success was very encouraging.

The Scottish Omnibuses Ltd. was then approached because some of our patients live on the outskirts of Edinburgh and do not use the Corporation buses. A full-scale experiment for six months was started for those patients who required the help of a disc.

The total number of discs issued is 42. Of these, 5 were only temporary—e.g., for patients with lower-limb fractures, who had to travel to the department for treatment. At the completion of treatment these discs were returned.

25 patients expressed delight at the unfailing help and courtesy given by both drivers and conductors. 11 others were helped sometimes but not always. 6 patients reported no success, but 4 who were temporarily disabled had not used their discs because they felt embarrassed; the other 2 found that the disc was not recognised, and they did not try again.

This scheme has been so successful that we hope similar schemes will be introduced in other parts of Britain. We suggest that the same type of disc be used so that it will receive universal recognition as the badge of the disabled requiring help on public transport.

Among those who have kindly helped have been Mr. N. W. Butterworth, of Butterworths (Edinburgh) Ltd., Mr. A. Sim, of William Sim and Sons (Paints) Ltd., Mr. T. Glass, of the Edinburgh Corporation Transport Department, and Mr. J. G. Methven, of the Scottish Omnibuses. I am grateful to the staff of the outpatient department of the Astley Ainslie Hospital, and particularly to Miss Jean Waterston for her work on the discs.

HEALTH SERVICE ESTIMATES

THE Ministry of Health and the Department of Health for Scotland are asking the Treasury for £538 million to run the health service during 1959–60.[1] This is about £12 million less than they needed in 1958–59; but the fall is more apparent than real, for it is due to the change in the method of making the Treasury's contribution towards the local authorities' health services. Instead of making specific grants through the various Ministries (last year's grant through the Ministry of Health was £28 million), the Exchequer is to make a general grant direct to the local authorities, which they will be able to allocate at their own discretion. Apart from these services, the Ministries' estimate still does not represent the total expenditure on the N.H.S., for the estimate naturally makes allowance for other moneys, such as the contributions and charges collected from patients. Allowing for these "appropriations in aid" the money to be spent on the service in 1959–60 is estimated at £694 million, compared with £695 million in 1958–59 when the local-government services were included.

The allocations to the hospital and other services are undistorted by changes in local-government procedure and can more usefully be compared with last year's. Where there is a difference, it is almost always an increase. The largest is in the revenue account of the English and Welsh hospital boards —£381 million as against £363 million in 1958–59. In England and Wales the pharmaceutical services will claim another £2 million and the dental services £2⅜ million. The general medical services, even allowing for the recent interim 4% rise to general practitioners, show an unexpected, if modest, decrease of £360,000.

1. Civil Estimates for the year ending March 31, 1960. Class v: Health, Housing, and Local Government. H.M. Stationery Office. 9*s.* 6*d.*

Medical Education

A YEAR IN VITRO

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MOST clinicians who aspire to consultant rank are tempted at some stage to forsake the wards for a while and to concentrate upon a problem which, in the modern idiom, is basic or fundamental. A happy few are driven by a desire to pursue further some topic which originated at the bedside; others feel that a knowledge of clinical medicine by itself is insufficient, and that special experience in an ancillary field is desirable; still others believe that a year spent in a laboratory is a valuable experience, although they are not sure of the reasons. Whatever the motives, they all seek to improve the standard of medical practice, by learning afresh the lessons of scientific integrity and thereby becoming better qualified to make critical clinical contributions to knowledge.

Whether indeed a year in vitro in the midst of clinical training is desirable must always remain a matter of opinion, and those who are called upon to make the choice are not necessarily the best qualified to do so. The benefits can only be judged retrospectively, so that much reliance must be placed upon advisers, many of whom are likely not to have had such an experience. Also, a measure of courage may be necessary before embarking upon a project which has no direct clinical bearing, particularly for those whose interest above all is the care of patients. In the event, once the decision to break away has been made, it is rarely regretted; but much thought may be needed in deciding how, when, and where the year should be spent.

HOW

The sudden translation of a postgraduate from busy hospital wards to a laboratory bench is no mean upheaval. However accurate he may have tried to be in his clinical work, he realises that many diagnoses are made by inference, remedies are often empirical, and social factors frequently determine the management; in scientific work the variables may be no fewer but they are usually better controlled, and conclusions can be more readily reduced to absolute terms. His previous scientific training may have been inappropriate. For example, those of us who recollect the hours spent in mastering the intricacies of floral formulæ and diagrams, and whose biological horizon extended to the identification at a glance of, say, the shoulder-girdle of a spiny anteater or the bones of the front foot of a tapir fully realise that whatever we may have gained in memory training was at the expense of integrated biological science. His clinical apprenticeship, with its inevitable emphasis upon factual information, may have provided few opportunities for original thought. Against this background he contemplates the widely held view that real research can come only from a laboratory, and feels that he is entering a realm of supermen. He will soon find that humility is equally desirable in either sphere, and that both have as their ultimate aim the relief of human suffering. In time, he may find some consolation in a recent statement by the American Foundation that "the number of free-wheeling clinical investigators is probably no greater than the number of test-tube investigators becalmed in the doldrums of techniques and mechanisms".[1]

1. Medical Research: a Mid-century Survey. New York, 1955.

In order to obtain full advantage from an in-vitro year, the following are essential: adequate laboratory space and facilities, suitable supervision, freedom to plan, complete lack of responsibility for patients or their routine tests, and opportunities of meeting other investigators and studying their methods.

WHEN

Following qualification, four or five years are almost inevitably spent in clinical appointments with, in present circumstances, an additional couple of years of National Service. Hence postgraduates reach the age of about thirty before they are called upon to consider seriously any deviation from established custom. By this time they have acquired a higher qualification, are capable of dealing with the rough-and-tumble of hospital patients under supervision, and often have a remarkably wide if uncritical knowledge of their specialty; they may also have made some modest contributions to medical literature. They aim so to arrange their future that they will be fully equipped to assume consultant responsibility at the age of about thirty-five. One of their problems is to decide when, if it is thought desirable, to cut themselves off from the clinical stream. There is a great difference between doing this late and early. If, as so often happens, they defer it until they have had eight or nine years in civilian hospital appointments, they are able to approach the ordeal with equanimity. The extra years of training will have enabled them to study some aspect of their specialty, and an in-vitro year gives them the opportunity of pursuing their former studies in a wider field with a more critical approach and a better appreciation of the potentialities and limitations of laboratory techniques. Original work, usually with a strong clinical bias, is ordinarily started during the registrar and early senior-registrar years by a process of infiltration, and by the time the in-vitro year has been reached the candidates have been thoroughly assessed from every aspect and their recommendation for such an appointment is completely safe. The younger postgraduates, with about four or five years in reputable appointments, have many disadvantages in terms of experience; but they have one supreme advantage—namely, adaptability. Their enthusiasm may be greater and their domestic commitments are likely to be less. If their power of criticism is immature, they are at the point at which this can be most rapidly developed. They have much in their favour, but their acceptance for appointment depends upon whether their abilities can be reliably assessed at this early stage and whether an experienced investigator with the necessary facilities is prepared to make room for someone whose contribution to his department is unlikely to be substantial. Surely an opinion upon their suitability can usually be given with confidence, and if they are capable of independent thought they will almost certainly have shown signs of it already. Hence the problem of selection is unlikely to cause difficulty. Whether facilities are available is an entirely different matter.

WHERE

If the year is to be undertaken early, selection of the correct type of training is the first consideration; this is much less important for more senior postgraduates, who have already decided where their interests lie. Despite the progressive integration of the medical sciences, two quite different mental approaches exist side by side—namely, the structural, in which most clinical deductions derive from visible data, and the functional, which is more closely related to physiology. The structural approach dominates in surgery, neurology, cardiology, hæmatology, and diseases of the chest and, in the laboratory, in morbid anatomy, cellular pathology, bacteriology, virology, and biophysics. The functional approach is more obvious in such aspects of internal medicine as endocrinology and diseases of the liver, kidneys, and pancreas, in which an appreciation of biochemistry demands a particular type of mentality. Both approaches obviously exist in every specialty, and in recent years the functional aspect has probably seen the greater advances. For example, thoracic surgeons, who a short generation ago were almost exclusively concerned with structural problems, are now hard put to it to maintain their patients in metabolic and cardiovascular equilibrium. In choosing between these two broad groups a postgraduate should ask himself whether he would be more at home with a microscope or a row of test-tubes; his decision is likely to colour the rest of his professional life.

Having decided upon the type of work he wishes to undertake, he will naturally seek an appointment with an experienced investigator who has the necessary facilities to offer. His first thoughts are likely to turn to the in-vitro groups under full-time professors in his own medical school. At first sight, these would seem to have many advantages: he is already known and his work can be adjusted to his capabilities; if he succeeds he enhances his chances of a more senior clinical appointment; and his local knowledge might shorten the initial period of bewilderment. On the other hand, professors vary in their ability to supervise the work of others, laboratory space may be short, and familiar surroundings may militate against original thought. Working with consultants who attend hospitals part-time rarely comes under consideration, unless the clinical aspect can be eliminated. Study at a centre of research away from a hospital might be entertained but these *vitra in vitro*, admirable as they are, are virtually inaccessible to clinicians in England. Hence, for practical purposes, the choice narrows down to work in a university department under a full-time director. The postgraduate with the necessary ability should be required to do no more than to indicate a suitable type of subject, and his teachers must be largely responsible for the ways and means.

So many postgraduates have visited North America in recent years that " a year in the States " has become part of their jargon. Despite the opinion of many who have not been there that such an experience is " unnecessary ", almost all those who have been agree that the year was the best or one of the best in their training. Quite apart from the advantages of acquaintance with the non-medical aspects of that remarkable country, the opportunities of knowing and proving oneself in a friendly yet alien atmosphere are unsurpassed. Laboratory facilities are often incomparably better than those at home, and most directors of departments set aside more time for postgraduate instruction. With so much care and attention given to those who have been properly qualified and recommended, the problem of when to go again arises. From conversations with many postgraduates on their return, the pattern of their reactions is evident. Those who go early are perhaps most impressed by the ramifications of medical science and the detail which is necessary in studying the simplest of problems. The older postgraduates seem to be more concerned with comparisons of techniques and academic standards. Doubtless these differences would have been apparent in similar groups working at home,

but, presupposing that each postgraduate intends to have only one in-vitro year and that the rest of his original work will be done part-time, which is the usual, timing is important. To embark upon a year of laboratory training in the United States with no more qualifications than about four years' experience in full-time junior clinical appointments is naturally hazardous, and might be construed as placing an unnecessary burden upon an active research department. As this is a matter of personal experience, an opportunity was recently taken to revisit the department concerned. The director hastened to point out that he had always welcomed postgraduates who were properly recommended, that his assistants covered a wide range of seniority, and that he tried to ensure that each was given a task appropriate to his ability. He was perhaps fortunate in having almost unlimited laboratory facilities, but his assistants were also fortunate in each having regular sessions in which their problems were discussed with him alone.

Discussion

The postgraduate training of potential consultants must always be primarily concerned with the practice of medicine. Concurrently, some experience of the more scientific aspects is inevitable. In the past, this has often consisted in studying specific clinical problems. Now the biological sciences are advancing so rapidly that more and more clinicians feel that they cannot afford to neglect training in laboratory methods, and many are tempted to spend a year in vitro, fully realising that a shorter time would be unlikely to be profitable. Whether this should be undertaken early or late ought to depend primarily upon the purposes of the year, which are to become reacquainted with scientific thought and to learn basic techniques with a view to their application in later life. In practice, the year is often insinuated at the least inconvenient time in relation to clinical appointments, and this is likely to be late rather than early. In other words, many postgraduates embark upon the year after having devoted a considerable amount of their spare time to clinical projects without ever having come face to face with fundamental realities. They are often so immersed in the clinical field that they are no longer able to adapt themselves to a different way of thinking, and may be tempted to spend much of the year looking over their shoulders at clinical colleagues. Surely this is putting the cart before the horse. The aim should be to select suitable men as early as possible—probably in the fourth or fifth year of clinical appointments—and to enable them to study in a scientific environment in order that their contributions to knowledge from the stage of senior registrar onwards may be based upon a solid foundation.

If this argument is sound, as indeed it seems, more laboratory space must be provided to advance or even maintain our standards of clinical medicine. Greater tolerance towards the uninformed will also be necessary on the part of some directors. Perhaps one of the most important provisions is an adequate salary for promising postgraduates. At this stage they are likely to be earning about £800–£1000 a year, and a comparable salary with a greater number of appointments would give future consultants their best opportunity of striking a proper balance between the art and science of medicine.

Dialogues of Today

THE PURITY OF SCIENCE

SOCRATES: I understand, Eryximachus, that the great advances in medicine we were talking about the other day are due to the developments and applications of science. I suppose, therefore, that there is such a thing as science, but I am not at all sure that I know what it is. Tell me what you understand by it.

ERYXIMACHUS: I am surprised that you should question it, Socrates, for is it not generally agreed that this is a scientific age, and one in which only scientific truths are indisputable, and only the highest scientific qualifications are given unquestioned respect? But since I am a doctor, and therefore have no claim to be considered a scientist, let Delphicus explain these matters to you; for he has won the highest honours science can bestow.

SOCRATES: Come then, Delphicus, tell us what science is, and how it is distinguished from other human activities.

DELPHICUS: Science, Socrates, is the discovery of truth for its own sake, and it seeks it only in matters which are measurable, and usually by applying to such material the methods of experiment.

SOCRATES: Does that explain, then, why medicine is not regarded as a science?

DELPHICUS: Yes, indeed, for much of medicine deals with things which are not accurately measurable, and even when they are, the truth about them is not pursued for its own sake, but in order to prevent or cure disease. Medicine, therefore, is only in part science, and it is even then applied rather than pure science, which, as I have said, is concerned only to pursue truth for its own sake. Indeed, on the whole I should prefer to call medicine an art rather than a science.

SOCRATES: I suppose, then, that if a man accidentally discovers that one germ destroys other germs, that is pure science?

DELPHICUS: Certainly.

SOCRATES: And if later workers discover a method of extracting from such a germ a substance which can be used to cure diseases, that is applied science? Or does it perhaps depend upon what was in their minds at the time, so that if they make the discovery out of pure curiosity it is pure science, but if they have in mind its possible applications it is applied science?

DELPHICUS: Well, perhaps the distinction between pure and applied science is less clear-cut than I supposed, and it may be possible for a man to be both a pure and an applied scientist at the same time.

ERYXIMACHUS: May that not be true of medicine?

DELPHICUS: Theoretically, perhaps.

SOCRATES: If science is concerned with measurement, I suppose scientists will differ in respect of what they measure, and resemble one another only in their common interest in measurement.

DELPHICUS: Certainly.

SOCRATES: So that a scientist who measures earthquakes or the stars will not easily understand the work of one who studies germs or the reproduction of animals.

DELPHICUS: That is true.

SOCRATES: And one who is concerned with germs or reproduction will have more in common with a physician, who, we have agreed, is not a scientist, than with another scientist who studies earthquakes?

DELPHICUS: Yes.

SOCRATES: Does it not seem, then, that those you call scientists, Delphicus, are not people who possess a certain kind of knowledge, which they all share, but those who practise a certain technique, and that science is really a kind of art?

DELPHICUS: You always seem to twist things round so, Socrates; but you can't get away from the fact that the scientists have transformed the world.

SOCRATES: Not altogether for the better, it seems to me!

DELPHICUS: You should not blame them for that, for their vocation is to pursue truth wherever it leads them: what society does with their discoveries is not their affair.

SOCRATES: Is it difficult or easy to make scientific discoveries?

DELPHICUS: Difficult.

SOCRATES: And is it difficult or easy to see what will be the effects of such discoveries?

DELPHICUS: Often very difficult.

SOCRATES: And is any one as well equipped as a scientist to foresee such effects?

DELPHICUS: Nobody.

SOCRATES: And are scientists part of society?

DELPHICUS: Certainly.

SOCRATES: Would you agree, then, that if society does not foresee the effects of the discoveries of science nobody is more responsible for this than the scientists?

DELPHICUS: But you yourself have said, Socrates, that scientists often cannot understand one another's work. How, then, can the men who designed the final weapon be blamed for not foreseeing its effect on human reproductive organs?

SOCRATES: I blame no-one, Delphicus; but it seems to me that those who pursue science by measurement have forgotten man, whom medicine at least remembers; and that it is time we had a society for the advancement of human science.

Public Health

Vital Statistics for 1958

IN his latest quarterly return [1] the Registrar General gives some provisional figures for England and Wales in 1958. The live-birth rate was 16·4 (the highest since 1949, when it was 16·7) and the death-rate 11·7 per 1000 (11·5) (previous year's figures in parentheses).

The death-rates per million in the last quarter of 1958 from pneumonia and influenza were 599 (788) and 21 (462) respectively. Deaths from acute poliomyelitis in the first nine months of 1958 were 75, compared with 157 in the corresponding period of 1957. Accidental deaths were slightly lower at 3998 in the final quarter of 1958 (4120). Deaths from all forms of tuberculosis again diminished slightly in the first three quarters of 1958 and were 3293, compared with 3391 for the corresponding period in 1957: mortality from lung cancer, however, continued to rise and total deaths were 14,455 (14,004) during this period. There were 589 deaths from appendicitis (506) in the first three quarters of 1959, but only 16 from whooping-cough (87) and 36 from measles (95).

Deaths from maternal causes in the first nine months of 1958 numbered 247, compared with 267 in the same period of 1957. A map included in the return illustrates the variation in the maternal-mortality rates in the standard regions of England and Wales in the period 1955–57. Maternal mortality was highest in Wales and in the North Western and Northern regions, and lowest in the Southern, Eastern, and North Midland region. The death-rate of children under one year of age in England and Wales in the September quarter was 20 per 1000 live births, compared with rates for the Netherlands of 15, for the United States of America of 25, and for Italy of 50 deaths per 1000 live births.

At June 30, 1958, the population of England and Wales is estimated at 45,244,000, and this is expected to increase to 52,023,000 in 1998. The number of children under 15 in England and Wales as a whole increased by 72,000 in the year ending June 30, 1958, especially in Essex and Hertfordshire, which are counties with large New Towns: the total of children under the age of 15 in the City of London was 450.

1. Registrar General's Quarterly Return for England and Wales: quarter ended Dec. 31, 1958. H.M. Stationery Office. Pp. 28. 2s.

In England Now

A Running Commentary by Peripatetic Correspondents

ANY building with steps devoid of grippable handrails (ornate balustrades are useless) is a disgrace to its owner, its builder, and its architect—particularly the architect, because he is paid to think for the others and ought to know better. His unimaginative standard answer is that " he sees no need ".

No need? Every war and accident unfortunately increases the need. So does every medical advance that prolongs life and increases the number of healthy but no longer agile elderly people. When your turn comes to retire, do you want to be kept out of public libraries, museums, art galleries, just when you've got leisure and time to enjoy them?

And while we are on the subject, what about escalators? True these are usually equipped with moderately grippable handrails that move in step with the steps. But there's nothing to hold when you're decanted off the distal end. At the moment of transition from moving to stationary you have to relinquish the moving rail; and if you're at all tottery, you're sunk. A short fixed handrail at each end of the moving handrails would make all the difference to some of the Underground's clients.

* * *

Heaven forgive me, I am thinking of starting yet another scientific journal. The *Journal of Speculative Natural Philosophy* would publish promising but at present unprovable ideas that no current journal will accept. Proven facts will have no place in it except on an I-told-you-so basis. Occasionally a modestly self-congratulatory paragraph will encourage future contributors by pointing out that some now-substantiated speculation first appeared, tentative and hesitant but unashamed, in its receptive pages. Speculations can be as fanciful as you please, so long as they are plausible under specified conditions. No doubt some leg-pullers will gain access: there are limits to editorial vigilance, and expert referees, to whom too many things are impossible, are obviously " out ". It is not, however, unknown for hoaxers to invade far more sacrosanct pages. Better to let them all in here—at least they should be good for a laugh at the Editor's expense—than to keep out something that someday may raise the eyebrows of someone, somewhere, who can clothe the idea with reality.

For the consideration of a life annuity of £2000 (or $10,000, based on Miami: would travel) I'm willing to become the first editor of *J.S.N.P.* All I need is a sponsor to bear all running expenses. I can guarantee him plenty of fun for his money and I don't mind betting we'll get quite a crop of future Nobel prizewinners.

* * *

Last week I suggested that the length of a book review apparently varies inversely with the size of the book. Since then another example of the Law of Inverse Squares has occurred to me:

> The lateness of arrival at any appointment (in minutes) varies inversely with the distance covered to reach it (or possibly with the square of the distance, but further work is needed here).

Thus a man coming from, say, Edinburgh, to an appointment in London will give the matter careful thought, study various timetables, take taxis, ask policemen, and probably arrive a good hour and a half before the chap who lives just down the Central Line.

Take me, for example. At risk of revealing my identity let it be said that I am sometimes late in arriving at my hospital. Now in olden golden days, when a first-year medical student, I lived deep in rural England. I rose with the dawn and sprinted a couple of miles over dew-clad fields to leap aboard a slow meandering train which deposited me several hours later at a smoke-grimed terminus from which a 6*d.* bus-ride (change at Marble Arch) took me to my destination. This discipline allowed me to arrive regularly on time (9 A.M.) for the only period of my life. Change and decay led to a small house in the outer suburbs, and with smart electric trains every few minutes there was no sense of urgency. I usually got the next but three and was habitually half an hour late.

Married status made me a free agent (well, within limits), and being by nature lazy, my feet took me to a house-agent specialising in inexpensive central property, and for some years my home has been but a stone's throw (I threw one) from my place of work. I am now later than I have ever been before, and usually only depart at the telephone prompting of my ward sister. When she retires, bless her, it is doubtful if anyone will be able to get me there at all.

The ultimate consummation of the Law will presumably be when I am admitted (it is a psychiatric hospital), for, though the distance will then be zero, I shall always be there, or rather not there.

* * *

The simultaneous translation system—English, French, and German—was superb, yet I found the audience a trifle apathetic. In the train on the way back from the conference I asked a colleague for his frank opinion of my paper. He said he was sorry that he had not heard a word of it. He had switched to German, a language of which he knows not a single word, so as to be able to concentrate on preparing his own contribution.

* * *

I did not always enjoy my porridge. In nursery days I sometimes balked until I was allowed a horn spoon. Later my brother and I were given brown bowls with a large red and brown cock at the bottom, and it was encouraging to see the stalwart bird gradually coming into view as one plunged deeper and deeper. A supplement of butter and sugar was a treat usually reserved for sore throats. How delicious it was to watch the butterball slowly liquefy as it sank into the middle of the hot porridge and then to spoon on a good mound of soft brown sugar.

The horn spoon, the cock, and the butterball came back to me vividly the other day as I read an article on four little cœliacs who were "fed oatflakes". One of the children was given "169 g. oatflakes per day for three weeks, an amount almost impossible to consume ... High intakes of oats are not easily maintained, as the child becomes tired of the flavour and overwhelmed by the bulk of the food". We were *never* offered oats—that was for horses and chickens. We did not even eat oatflakes or oatmeal. We ate porridge, and oatcakes, and other nice things. I feel very unhappy about children being fed oats or oatflakes. Even "fed" has a nasty sound. At once you are in a laboratory, where men in slightly soiled white coats are forcing this and that into dwarf albino mice or adrenalectomised rats.

I should like to know what those children really ate and how. Did they eat porridge, or oatcakes, or what? Were they allowed sugar? Was the porridge hot or cold? In any further studies I shall expect clearer definitions of the terms used: oats, groats, rolled oats, oatflakes, oatmeal (fine, medium, or coarse), gruel, brose, and so on. And I shall place limited reliance on the findings unless it is stated plainly whether these quantities were achieved with or without the use of a horn spoon.

* * *

In the Garden–VI

IS YOUR GENTIAN A GENT?

It's no good telling me this or that makes *G. acaulis* flower.
I've given it that and this and studied it by the hour.
I've given it pigeon's dung and love and even royal jelly,
I've watched it through a reading-glass while lying on my belly.
I've tried Mars bars and consulted the stars and fed it with traces of boron,
Yet the girl next door, who's a beautiful bore and a horticultural moron,
Said, did I remember last September I gave her a bit of stuff,
And now her view is a sheet of bliew, she can never thank me enuff.

Moral

Of the sex life of *acaulis* I don't know very much
Perhaps my Gent. is just a gent and needs a woman's touch?

Letters to the Editor

DOCTORS FOR OVERSEAS

SIR,—I hope your leader and the depressing article "On Being Seconded" in your last issue will provoke constructive action by those who control our professional lives. I write not as one ensconced in an ivory tower around Senate House but as one who in the early '30s was a consultant at a London teaching hospital and also at a special hospital and relinquished these posts to take a chair at Hong Kong University. Those were the days of no return and no secondment, when mail took six weeks to reach us, and there was no air-conditioning; our wives took the plunge with us.

Although many previously British overseas possessions are now independent, there is still a demand and respect for teachers and research-workers from this country. If this supply is to be maintained, and with it British prestige, influence, and culture, then our universities, the Ministry of Health, and the Colonial Office must move quickly and energetically; for it is later than we think, and other countries will displace us with detriment to ourselves.

The universities of Minnesota and California have established themselves *in loco parentis* to the universities of Korea and Indonesia. There is secondment of professors and others, attachment of postgraduates from the Asian universities, and a free and active exchange at all levels. In this country at least we might effect a compromise. For instance, the department of surgery at St. Christopher's might take an avuncular interest in the same department at Hong Kong University; the physiology department at Bentham College in University College, Ibadan; the obstetric department at St. Anthony's in University College Hospital of the West Indies; and so on.

The white-cliffs-of-Dover horizon and the complacency it engenders is dangerous and deadening. We make haste so slowly that we are already being bypassed in favour of U.S.A., West Germany, and Russia.

University College Obstetric Hospital, London, W.C.1. W. C. W. NIXON.

FAILURE OF STERILITY IN HOSPITAL WARD PRACTICE

SIR,—Professor Hare (April 4) questions whether the transfer of sterilising work from an unsatisfactory ward boiler to an unsatisfactory autoclave is likely to lead to any improvement in sterilising practice or any reduction in cross-infection. But why were the boilers and the autoclaves unsatisfactory? The recent investigations undertaken by the Nuffield Trust attribute their failure to the following causes:

(*a*) Autoclaves and boilers were widely distributed under circumstances in which supervision and control were impossible; and

(*b*) where supervision and control of the autoclaves were possible, responsibility was ill defined.

If central sterile supply departments were to be established in hospitals such causes should disappear. There would then be no ward boilers, whilst the autoclaves would be concentrated where supervision and control are simple and responsibility is clearly defined. Whether such measures would reduce the level of cross-infection it is impossible to say. But certainly *Clostridium tetani* and *Cl. welchii* should disappear, as also should most of the organisms found by Dr. Darmady. Is the killing of such

organisms as unimportant as is suggested? Professor Hare advocates the retention of ward boilers "because they should form an important part of the education of nurses and medical students". Has the training of nurses in sterilising syringes suffered since the introduction of syringe services? Could not nurses be taught to improvise when the facilities provided in their schools are no longer available?

There is also another most important factor. Syringe services, where established, meet with the unanimous approval of the nursing staff because they no longer have to perform the tedious task of sterilising syringes.

With the introduction of the 44-hour week for nursing staffs the question of whether the standard of patient care has been lowered is a matter of conjecture, but it has certainly led to the streamlining of many nursing techniques used in patient care. The central sterile supply departments would further lighten the load of nursing staffs and enable them to devote more time and service to the bedside care of their patients. This would certainly be appreciated in many regional hospitals which, unlike Professor Hare's own hospital, are not blessed with the same high ratio of nursing staff to patients. The importance of removing work which can be more satisfactorily done in other departments from the nurse on the ward so that she may devote more time to the care of her patients cannot be overemphasised.

J. REVANS
Chairman, Advisory Panel, Nuffield Trust Investigation into Sterile Supply Arrangements for Hospitals.
Durley, near Southampton.

SIR,—Professor Hare states that most of the infections in hospital are due to organisms on the fingers and clothing of nurses and doctors. He might have included blankets.

On beds in hospitals in the United Kingdom at the present time there are many millions of blankets. The life of one blanket (washed perhaps twice a year) is about ten years. To replace these blankets by cotton "blankets", which can be boiled in the laundry, "at one fell swoop" would be an expensive operation; even with such a good "blanket" as the Ashton terry weave. Also, there would be political repercussions in that the Australian wool industry would suffer (even more if the cotton "blanket" spread to other countries).

As an economic proposition it seems that some cheap and effective method of sterilising the woollen blanket is required at once. A variety of methods are now available. The one I favour is cleansing in 1 : 200 'Lissapol', followed by rinsing and partial drying in a centrifuge (spin-dryer), followed by soaking in 1 : 200 'Fixanol C', and drying without further rinsing. Some efforts have been made to replace fixanol C with 'Cirrasol OD', but the latter substance is disappointing.

The objection to this lissapol and fixanol method is the high cost of the extra labour. These extra costs could be obviated by a substance which would combine the two treatments lissapol and fixanol in one operation. Such a substance is 'Hytox' (Domestos). Unfortunately this substance is not so powerful a bactericide as is desirable; but this could be improved perhaps by molecular additions.

Other possibilities are to use an additional substance in the rinsing-water; such a substance could be dilute chlorhexidine, which would supply antibacterial reinforcements. No extra labour would be involved, since rinsing would have to be performed in any case. Another device which would reinforce the antibacterial effects of any cleansing operation would be to wash the blankets or rinse them in water at 60° C. This is far short of boiling, which is known to damage blankets, but is hot enough to kill *Pseudomonas pyocyanea*, which may be troublesome. There are a number of other substances which can be added to the rinsing-water to reinforce bactericidal manœuvres without adding to labour costs.

To prevent infection by fingers "gloves for nurses" seem to be indicated.[1] The lesson seems to be further reinforced by The Story of the Shipyard Eye.[2]

Epping. FRANK MARSH.

DEATH FROM TONSILLECTOMY

SIR,—Were routine blood-tests to be done on all candidates for tonsillectomy they would be worse off, not better. Diamond and Porter [3] have shown that these tests are not merely a waste of time, but are often misleading; and Fletcher [4] has come to the same conclusion.

Precisely the same argument holds for the investigation of bleeding tendency in patients who need tooth extraction. For many years it has been my practice to interview all these patients myself, take a detailed history of their bleeding tendencies, and do such laboratory tests as seem likely to be profitable. In practice, 9 patients out of 10 need no laboratory tests; and the occasional patient with a real bleeding tendency stands out like a lighted candle in a coal-cellar.

This procedure is advocated by Diamond and Porter, and by most of the experts on clinical hæmostasis with whom I have discussed the problem; but of course it presupposes an intimate knowledge of the natural history of all the bleeding diseases, which is more often possessed by the clinical pathologist than the surgeon.

Central Middlesex Hospital, London, N.W.10. GEORGE DISCOMBE.

SIR,—Dr. M. E. N. Smith's article (March 28) is most courageous. He rightly concludes that the operation is unjustifiable. The Medical Research Council,[5] 21 years ago, described it as "a prophylactic ritual carried out for no particular reason with no particular result", but this has exerted little influence on teaching at medical schools.

When a parent brings a child to the surgery, the usual routine is to take a history from the mother, examine the child, and discuss the case with the parent. The child is rarely asked about his symptoms directly, and the meaning of the illness, what it does to and for him, never elicited. In a paper [6] on the catarrhal child I showed that the attitude of parents determines whether the child coughs and splutters his way happily to school or is a constant attender at surgery. The utilisation of the child's symptoms by the parents or child is the prevailing factor. The catarrhal child, as seen in practice, has attached to it a parent with free-floating anxiety, ostensibly related to the child's condition.

Dr. John Apley (March 28) states that "the parents of a child with symptoms *should* worry, and should go on worrying until he is better". He fails to perceive that this worry is both causative of the child's condition and a plea for recognition by the doctor of their own anxiety and guilt. The acceptance of the mother's overt anxiety as a direct result of the child's symptoms and the neglect of her own emotional problems result in reattendances. Her related deeper anxieties remain unrecognised and indeed neglected. "The child is the presenting symptom of the mother".[7] Her continuous anxiety, despair, guilt, and agitation, albeit belied by the appearance of the child, becomes transferred to the practitioner, leads to the seeking of further advice and treatment—the dilution of responsibility—so as to relieve the child, the parents, and the doctor from an accumulated tension. In my own practice the primary reason for my referral and admission to hospital of children with varying phases of sino-laryngo-tracheo-bronchitis was my own anxiety about prognosis. The amount of anxiety was related more directly to the agitation and despair of the

1. Marsh, F. *Lancet*, 1958, ii, 588.
2. Jawetz, E. *Brit. med. J.* April 4, 1959, p. 873.
3. Diamond, L. K., Porter, F. S. *New Engl. J. Med.* 1958, **259**, 1023.
4. Fletcher, R. *Laryngoscope*, 1958, **68**, 1087.
5. *Spec. Rep. Ser. med. Res. Coun., Lond.* 1938, no. 227.
6. Nichols, L. A. *J. Coll. gen. Pract.* 1959, **2**, 43.
7. Balint, M. The Doctor, the Patient and his Illness. London, 1957.

parents than the course of the illness. Psychotherapy for the parent was the answer, not wholesale reassurance; because reassurance with explanation helps a few parents, but not all, For only the G.P. will notice the reattendances of mothers with new complaints referred to themselves, other children, or their husbands after the mutilating sacrifice of the child's lymphoid tissues or the cessation of enuresis by the use of electrical apparatus.

I am able to learn some part of this psychotherapy by attending seminars for general practitioners at the Tavistock Clinic. This privilege is denied to practitioners from the provinces by the refusal of the British Postgraduate Medical Federation to allow their claims for the usual allowances, an attitude admirably criticised by Dr. Lask (March 21). Learning of my own deficiencies, automatic responses to patients' demands, my inability to tolerate their depression, anger, and anxiety has helped my work and my patients' health. If we are to understand our own self-centred interests; if we are to refrain from disparaging criticisms of the valuable report of the Central Health Services Council on the welfare of children in hospital and concentrate on keeping children out of hospital; if we are to avoid exposing children to the horrors of adult wards; if we are to have as much sympathy for a child's mind as we have for knock-knees or normally enlarged lymphoid tissues, then the primary change must come from newer methods of teaching, doctors as well as students. Psychological medicine as taught by the psychoanalytically trained must be afforded its rightful place.

Sidcup, Kent. LOUIS A. NICHOLS.

CHILDREN IN HOSPITAL

SIR,—Dr. Elizabeth Tylden's letter of April 4 has spurred me to comment upon the report on the welfare of children in hospital. Like the majority of my pædiatric colleagues I have been impressed by the realistic and balanced views of the committee, although I was concerned about the contents of paragraph 34; my uneasiness has not been lessened after reading Dr. Tylden's letter.

The majority of pædiatricians are fully alive to the difficulties that confront parents when their child is admitted from a distance and they realise the time taken to travel to the hospital and the expense involved. It is to meet these two points that Dr. Tylden supports the development of small wards (10 beds) in general hospitals.

The young child in hospital, having been removed from the people and environment he knows, will fret or cry or be happy when his parents are not present and it will make no difference to him whether they live three or fifteen miles away unless the shorter distance means that his mother will stay nearly all the day or will actually live in hospital. Living-in facilities are more likely to be provided in a children's hospital or large children's unit and from my experience prolonged daily visiting will not readily be approved for a small unit in a large general hospital. In addition:

(1) One has the difficulty and expense of finding an adequately trained nursing staff for such small units.

(2) The immediate medical supervision would almost certainly be the responsibility of someone whose main appointment is to a general medical or surgical ward and who may not have had any pædiatric experience.

(3) The consultant in charge would be some distance away and not always available to help with an emergency.

(4) The ancillary departments of the hospital (laboratory, biochemical, and radiological) would not be geared to handle young children satisfactorily.

It is the responsibility of the medical profession to treat as many young children as possible at home and much effort should be made to achieve this object. Failing this, children should *not* be treated in adult wards or tiny wards in general hospitals. They should be looked after in a children's hospital or unit with a high standard of pædiatric practice which is adequately staffed at all levels, where there is a tradition of sensible child-care, and where considerable effort has been expended in establishing a good parent-hospital relationship. I am confident that the majority of parents would prefer their children to enter such a unit and would be prepared to shoulder the extra physical and financial burdens that might occur.

Manchester. GEORGE KOMROWER.

THE CHROMOSOMES IN MAN

SIR,—The recent reports of chromosome abnormalities in man will increase our understanding of human genetic mechanisms, and further information can be obtained from a study of these cases in which sex-linked recessive characters are also present.

The colour-blind patient with gonadal dysgenesis [1] had been studied cytologically. She has a heteroploid bone-marrow with only 45 chromosomes, and her parents both have a normal chromosome number.[2] The patient and her brother suffer from extreme deuteranomaly of regular type, her father has normal colour-vision, and her mother shows a minor defect on anomaloscope testing, which is in accord with the view that she is a heterozygote.[3] These data strongly suggest that the defect has arisen in consequence of an abnormality of spermatogenesis.

An abnormality of oogenesis could explain a case of gonadal dysgenesis with a colour-blind father,[4] and the possibility of a mosaic is suggested by the report of a patient with irregular deuteranopia[5] who is chromatin-negative.[6] The report of colour-blind patients with chromatin-positive Klinefelter's syndrome [7] suggests a defect of oogenesis with abnormality of the second meiotic division, but a large series of colour-normal cases [8] suggests that some are due to an abnormality of the first meiotic division of either oogenesis or spermatogenesis.

Glasgow. JOHN S. S. STEWART.

HAZARDS OF WATER ENEMAS

SIR,—I should like to add a point to your leading article of March 14. The absorption of large quantities of hypotonic solution may cause disorders simulating encephalitis in addition to the usual and well-known symptoms of "water intoxication". Diagnosis may be difficult, for none of the references on the subject mentions the possibility of confusion with encephalitis.

We have recently observed a 4-year-old boy with congenital megacolon. To cleanse the bowel of contrast material after a radiographic examination in another institute, tap-water enemas were given. The 8 to 10 litres instilled had seemed to return completely. As late as eight hours thereafter slight restlessness, sweating, nausea, and vomiting developed. Considerable quantities of dilute urine were passed. The symptoms were relieved for a while by intravenous isotonic glucose and Ringer's solution. A few hours later he was unconscious with clonic convulsions of arms and legs. Soon deep coma, generalised tonic convulsions, carpopedal spasm, and muscle rigidity followed. The tendon reflexes were exaggerated and there was a slight facial palsy on the right side. The temperature rose to 39° C (102·2° F) for several hours, but the cerebrospinal fluid was normal.

1. Stewart, J. S. S. *Lancet*, 1958, i, 161. (Cited by Ford et al. *Lancet*, April 4, 1959, p. 711.)
2. Jacobs, P. A., Stewart, J. S. S. (In preparation.)
3. Pickford, R. W. *Advanc. Sci.* 1958, **15**, 104.
4. Frey, R. G., cited by Walls, G. L. *Arch. Ophthal., N.Y.* (in the press).
5. Walls, G. L. *Amer. J. Ophth.* 1955, **39**, 8.
6. Walls, G. L. Personal communication. 1958.
7. Nowakowski, H., Lenz, W., Parada, J. *Klin. Wschr.* 1958, **36**, 683.
8. Polani, P. E., Bishop, P. M. F., Ferguson-Smith, M. A., Lennox, B., Stewart, J. S. S., Prader, A. *Nature, Lond.* 1958, **182**, 1092.

The continuous seizures were not controlled by repeated injections of barbiturates, chlorpromazine, and calcium gluconate. Salt infusions and artificial hibernation to 34·6°C (95°F) for thirty-six hours finally relieved the grave situation.

In the next ten days the convulsions did not recur, but some muscle twitchings were seen. Moderate intellectual impairment, a slow, hesitant, syllable-by-syllable speech, a severe intention tremor of the hands, and an ataxic walk with flaccid paresis of the right foot, resembling peroneal palsy, were present. From the tenth to the twentieth day the patient improved gradually and on the thirtieth day only slight symptoms persisted. Recovery of mental condition, intelligence, speech disorders, facial and peroneal paresis, ataxia, and tremor was complete two weeks later.

In view of the grave convulsions, the fever, an elevated erythrocyte-sedimentation rate, and the neurological and psychological changes, the condition was first diagnosed and treated as encephalitis. The normal cerebrospinal fluid, reduced plasma sodium and chloride levels in the acute stage, and the rapid and complete recovery, however, made it clear that water intoxication had been overlooked. The neurological symptoms were apparently a rare consequence of the reduced osmolarity.

1st Department of Pædiatrics,
University Medical School,
Budapest.

MAGDA KOCSIS

CARBROMAL INTOXICATION

SIR,—Your issue of April 4 containing an account of chronic carbromal intoxication by Dr. Copas and his colleagues came to me two days after I had been confronted with such a case in consultation.

The patient was a woman of 55, with no known psychiatric history, whose married daughter came home for a visit and found her mother off her food and behaving strangely. The patient admitted taking 'Relaxa Tabs' for sleeplessness in considerable numbers. Her blood-bromide on April 4 was 170 mg. per 100 ml., and after a week without her tablets, she has become mentally normal.

May I add my voice to the suggestion that carbromal should not be sold without a prescription.

St. Helier Hospital,
Carshalton, Surrey.

C. P. PETCH.

INTERSTITIAL INGUINAL HERNIA

SIR,—I was very interested to read Mr. Cundall's letter of March 28. In 1950 I described [1] 6 cases of interstitial hernia out of a total of 482 inguinal herniæ personally operated on at St. Luke's Hospital, Anua, within twelve miles of Mr. Cundall's hospital.

The reason why a sac should become interstitial has not been established. It has been held since the days of Krönlein that the cause is an obstruction in the inguinal canal or at the external ring. The commonest cause suggested is an undescended testis. This is said to explain the preponderance in the male. Lower and Hicken [2] collected 590 published cases and found that the ratio of male to female was 4 to 1. Such an obstruction, however, would not explain the inguino-superficial type (Küster's hernia) where the interstitial sac lies between the inguinal ligament and Scarpa's fascia.

The importance of these herniæ is that the properitoneal type—i.e., where the sac lies between the peritoneum and fascia transversalis—can rarely be diagnosed preoperatively. Even when strangulated they are usually diagnosed as an internal obstruction since a mass is not usually palpable.

County Hospital, Cashel,
Co. Tipperary.

T. J. NOONAN.

1. Noonan, T. J. *Lancet*, 1950, ii, 849.
2. Lower, W. E., Hicken, N. F. *Ann. Surg.* 1931, **94**, 1070.

ISRAEL: THE EVOLUTION OF AN IDEA

SIR,—Dr. Symonds' articles were interesting. But I am struck by the new tragedy, that as a result of the U.N. partition resolution on Palestine in 1947, there are now nearly a million displaced Arab refugees on the borders of Israel.

If they were of Jewish faith, rather than Christian (10%) or Moslem, they would be allowed to return to their homes and land in Israel tonight. In his book, *A Study of History*, the historian Prof. Arnold Toynbee wrote:

"... the Jews had even less excuse in A.D. 1948 for evicting Palestinian Arabs from their homes than Nebuchadnessar and Titus and Hadrian and the Spanish and Portuguese Inquisition had had ... In A.D. 1948, the Jews knew from personal experience what they were doing; and it was their supreme tragedy that the lesson learned by them from their encounter with the Nazi Gentiles should have been not to eschew but to imitate some of the evil deeds committed against the Jews."

From the latest report of the director of the United Nations Relief and Works Agency for Palestine Refugees (UNRWA) we learn that they are existing on 1500 calories a day. May I quote the report on the subject of repatriation and resettlement:

"There have been no signs of any changes from their collective hostility towards major development projects which, to the refugees, imply permanent resettlement away from their ancestral homes and the abandonment of their hopes of repatriation. Nor has there been any affirmative action by the Government of Israel to facilitate the implementation of General Assembly resolution 194(III) of 11 December 1948 concerning repatriation and compensation."*

These quotations speak for themselves. I will not uncover any more of this inflammatory area with further comment.

London, W.1.

ROBERT JOHN.

SIR,—I read the two articles by Dr. Hedy Symonds in your issues of March 7 and 14 with mounting amazement. At first sight one hardly knows what to make of such a sequence of analytic equivocations coupled with a disregard of world Jewish history and its ideals and aspirations. The attempt to psychoanalyse the Jewish National revival and its achievements is the more of a travesty in that it ignores the blood and sweat and tears that have gone into the making of the new Israel: in places it becomes almost an insult to those who suffered and gave their lives in the process.

The allegorical-symbolic method can be made to "prove" anything, as Janet pointed out many years ago. If one event does not cause its sequence, then the sequence must be a reaction to it; or one gets out of it with an ambivalence.

Here are one or two of the psychological theses delivered ex cathedra, as if self-evident or proven:

"The mutual attraction of people with such different backgrounds (Jewish and German) can be understood psychologically."

"If people stand vis-à-vis as persecutor and persecuted, each must (sic) absorb the mentality of the other. ... Just as the persecutor acquires some doubts about the guilt of his victim, the persecuted begins to doubt his innocence" (this apropos of the Nazi attempt to exterminate the Jews).

And to explain the Kibbutz movement:

"The members of the kibbutz, having been intellectuals and comfortably off, became peasants and penniless. Nurtured on

* "The General Assembly ... 11. *Resolves* that the refugees wishing to return to their homes and live at peace with their neighbours should be permitted to do so at the earliest practicable date, and that compensation should be paid for the property of those choosing not to return and for loss of or damage to property which, under principles of international law or equity, should be made good by the Governments or authorities responsible."

anxious parental love, their ideal became the impersonal hygienic care of children in separate children's homes."

They are all so confidently tripped off, yet on closer inspection I find the first statement is meaningless, the second is palpably untrue, and the third pure speculation and supposition. It is not borne out by my close acquaintance with members of the Kibbutz movement, many of whom I have known intimately, both before and after their arrival in Israel.

Much light is thrown on Dr. Symonds' pyschological values on pp. 572–3, where the natural doubts and self-criticism of the Israelis are made out as neurotic manifestations: the sign of normality is " single-mindedness ". The curious conclusion is then derived that in the organisation of its army Israel is " departing from a neurotic pattern " and behaving more rationally. The same argument is applied to the country's superhuman efforts to take in new immigrants—which I am afraid no economist would call at all rational. It is part of the Jewish ideal embedded in their world history, and as such is beyond Dr. Symonds' psychology.

I will not go into the application of this kind of psychology to Jewish religious issues; that attempt has been made before and failed. Need I say how much I disagree with the definitions of religion—" the emotional and irrational components of human nature "—and science.

One fallacy in particular must be pointed out. The attempt to explain Jewish values—in or out of Israel—as some kind of reaction to German Nazism can be refuted by a nodding acquaintance with Jewish history and ethnography. The Jews of Germany never accounted for more than a small fraction of world Jewry, and from the point of view of the tradition, by no means the important one. This latter position, by general consent, was for the past 300 years held by Russian-Polish Jewry: before that we had the French Rhineland, and before that Spanish Jewry, and so on. The Jews of the other 69 of the 70 nations which Dr. Symonds mentions at the end will, I am sure, have far more to say in the final outcome than the ex-Germans.

I too have worked professionally in Israel. I know enough of world Jewish history and its traditions to make me alive to their presence and continuing influence in the country of Israel. Apart from an odd item here and there, for all that we are really given about Israel, the two articles might well have been written in the analytic consulting-room. They are eloquent chiefly of the shortcomings of psychoanalytic " explanations " when applied to matters outside their proper context.

Israel is not just an idea, and certainly not a neurotic one. It is a very practical going concern with real empirical problems which it is tackling energetically, and to which these articles do but scant justice.

H. EDELSTON
Lately consulting psychiatrist to Youth Aliyah (Youth Immigration Department) in Israel.
Leeds.

SIR,—The article by Dr. Hedy Symonds (March 7 and 14) was interesting, but contained some assumptions and deductions which are erroneous. She stated (p. 573):

" One reason for the apparent return to religion—official religion—in the United States and Britain is the belief that religion was the force that prevented creation of materialistic dictatorships in these two countries, and that morality's tenuous hold on humans cannot be strengthened, and emotional satisfaction gained, except through accepted forms of religious adherence. This particular attempt at reconciling the rational and scientific with the irrational and subjective is as yet in its infancy. But the force of conviction is lacking; the religious revival sits uneasily even on official functions, nor is it successfully accomplished in the individual."

Dr. Symonds then goes on to point out that " this crisis of religion is even more evident in Israel ".

The man whose religion is an intimate part of his nature does not adopt religion as an expedient to prevent dictatorship in his country, to strengthen the controlling influence of morality, or to gain emotional satisfaction, but because he believes in Almighty God who has created him. Nor is his religion either (*a*) irrational, because it happens to embrace both material concepts which are in the sphere of science as well as spiritual concepts which are in the sphere of theology, or (*b*) subjective, because it involves him in relation to his Creator. Moreover, it is very much a debatable point as to whether " the religious revival sits uneasily even on official functions ".

It is not correct to assume, as has been done, that the return to religion is " apparent ". To many of us who are Roman Catholics in this country, the adjective to be applied is not " apparent ", but " evident ".

In the paragraph following the one quoted above, Dr. Symonds stated, with reference to a " militant minority " of immigrants who " free from intellectual doubt can act with the emotional conviction of crusaders ", that " they are the more vociferous equivalent of those who, in other lands, can see only outworn forms as answering present needs ". Surely it is extremely incautious to apply the term " outworn " to forms, presumably of religion, used with conviction by people in other lands, without either specifying the nature of these forms, or stating that they are outworn only in the opinion of the writer.

M. E. CARPENTER.
Redhill.

ALDOSTERONE EXCRETION IN NORMAL PREGNANCY AND PRE-ECLAMPSIA

SIR,—Dr. Kumar and his colleagues (April 11) have failed to remove the " misunderstanding " that prompted my criticism.

They had earlier shown a definite effect of a *lowering* of the intracellular sodium that accompanied a *rise* of aldosterone secretion in normal pregnancy when salt was restricted. If this finding has relevance in the context of their hypothesis it must be assumed that aldosterone reduces the intracellular sodium content. Yet a *rise* of aldosterone secretion which they found to accompany toxæmia produced a *rise* in the intracellular sodium. Should they maintain that aldosterone brings about an increase in intracellular sodium, how then do they explain their earlier finding where its increase lowered the intracellular sodium content?

Most data have hitherto indicated a fall both in the formaldehydogenic steroids and aldosterone levels as toxæmia mounts—findings that Dr. Kumar and his colleagues appear to contradict.

JOHN SOPHIAN.
London, W.1.

PSYCHOGENIC FEVER

SIR,—I have often noticed with dismay the expression of discredit shown by some doctors when the subject of psychogenic fever is discussed. It was particularly consoling and refreshing to read Dr. Malleson's article (Jan. 31) on panic and phobia in which he so clearly described such a fever.

Then came the fearful disillusionment in the letter from Dr. Goodall (March 21). Dr. Malleson had a premonition when he added in parenthesis, " Some people do not recognise psychogenic fever in adults. I am sure they are mistaken." I am prompted to write because I too am " sure they are mistaken ".

Examination fever is a very real one, experienced, yet not accepted, by many. I have seen much of it and I have seen fevers in young adults in many diverse situations, commonly in those sportsmen in a second eleven who have a possible and doubtful chance of a place in the first, and in young adults involved in religious instruction.

It seems that many doctors dislike making a positive clinical diagnosis (i.e., recognising an elephant as an elephant) of a psychogenic fever. It is considered an inadequate one, and therefore it behoves such a doctor to disregard the patient's natural reaction to fear as the cause of the trouble and to nominate instead some virus or bacterium as a more respectable and generally acceptable ætiological agent.

The implications of this situation are many, but one of the most important is the almost inevitable instigation of chemotherapy which, the diagnosis still being incorrect, will probably be repeated in the same patient (in variation form) in some similar future situation, bringing with it all the possible dangers of such recurrent therapy.

This reason alone surely suffices to re-emphasise the importance of the recognition of a psychogenic fever as a psychogenic fever.

Derby. D. W. S. SHELDON.

ANASTOMOSIS IN THE CORONARY CIRCULATION

SIR,—I should like to comment further on a suggestion by Professor Blumgart and Dr. Zoll (Jan. 24) that our findings of coronary anastomosis in normal individuals were due to faulty technique. Your readers may be interested in the work of Vastesaeger et al.[1]

They looked for intercoronary anastomoses in several mammalian species by a perfusion technique and by hyperstereoscopic radiography after injection of iodised oil. Anastomoses were demonstrated in calves, pigs, sheep, horses, and dogs. The diameter and frequency of the anastomoses differed from one species to another and from one subject to another in the same species.

The coronary arteries of 7 human fœtuses or newborn children were also injected and radiographed. Arteriolar anastomoses were observed in 6 hearts.

Arteriolar anastomoses were discovered in 80% of 120 adult human hearts. The diameter of these anastomoses was 1 mm. or more in 7·5%. The frequency of anastomoses did not seem to be higher in patients with coronary disease than in those with normal hearts.

Observations in animals and human fœtuses, free of any coronary narrowing or occlusion, emphasised that, anatomically, intercoronary anastomoses are congenital. Arteriosclerotic occlusion cannot create new coronary connections, but Vastesaeger et al. suggest it may incite a functional hypertrophy of pre-existing anastomotic vessels.

Perth, Western Australia. W. LAURIE.

EFFECT OF ALTITUDE ON LEUKÆMIA

SIR,—The well-known lytic action of glucocorticoids on lymphoid tissue seems to account for the good results with cortisone and similar therapy in lymphatic leukæmia. This effect is not found in myeloid leukæmia, in which even large amounts of corticotrophin (A.C.T.H.) do not decrease the number of circulating leucocytes.[2] In these patients there may be a temporary improvement in general condition and in the accompanying hæmolytic anæmia (which is not rare in chronic lymphadenopathies); but, in general, myeloid leukæmia is not an indication for treatment with glucocorticoids.

Because of the invigorating effect of mountain climate, patients with leukæmia were sent to our institute, which is 1000 metres above sea level. Any other treatment they were having was continued.

In 17 cases out of 21 observed, there was a definite deterioration ten to fourteen days after the change in altitude. The output of urinary mucoproteins (determined with toluidine-blue)[3] usually showed a significant rise following the increase of leucocytes within five to seven days. This observation can be explained by the augmented destruction of shortlived immature elements, containing polysaccharidoproteins. Loss of weight, fever, and tiredness were common, but there was no tendency to hæmorrhage. A myeloblastic crisis developed in 4 cases out of the 17.

1. Vastesaeger, M. M., Van der Straeten, P. P., Friart, J., Candaele, G., Ghys, A., Bernard, R. M. *Acta cardiol.* 1957, **12**, 363.
2. Schwendy, J. *Z. ges. inn. Med.* 1957, **12**, 779.
3. Albeaux-Fernet, M., Bugard, P., Romani, J. D. *Pr. méd.* 1955, **63**, 509.

As the patients were from places 200 metres or less above sea level, an abrupt change of 800 metres or more can be considered an intense stress. In such a change, the increased excretion of neutral 17-ketosteroids points to suprarenal activity.

The slight hypoxia and the need to adapt to barometric change, followed by increased glucocorticoid production, seems to be a powerful stimulus to the bone-marrow. This stimulation, beneficial in different anæmias, seems definitely dangerous to patients with myeloid leukæmia.

Laboratory of St. Kúpele, Nový Smokovec, Czechoslovakia. J. KELLEN.

SOFT DRINKS

SIR,—Dr. Bicknell (March 14) expresses concern over "secret" soft drinks and especially mentions American "cola" drinks.

I have been associated with the analysis of U.S.A. cola drinks over many years and your correspondent would probably like to know my findings. They contain orthophosphoric and citric acids, extracts of cola and vanilla, added caffeine (about gr. 1/4 to the 6 oz. drink), sugar, caramel, salt, CO_2, and commonly used essential oils, seven-eighths of which are citrus oils and the remainder spice oils. The drinks are sterile and contain no artificial preservative. In caffeine content they are equivalent to weak tea and they are undoubtedly safe and wholesome, while being truly thirst-quenching.

Johannesburg. ERNEST GEORGE.

GAMETOID THEORY OF CANCER

SIR,—In 1906, more than 50 years ago, as cancer research scholar at the London Hospital in 1904–5, I furnished a report[1] in which a theory as to the nature of the malignant process was outlined. This was based on the important work of Farmer, Moore, and Walker (described in a paper read before the Royal Society on Dec. 10, 1903). Since then, on several occasions, I have reiterated the same idea. Over the years I have seen no more satisfying (to me) explanation of the cancerous process. Now that it has been seriously suggested that malignancy is due to a mutation in somatic cells, it seems worth while again calling attention to this theory as it gives, I think, a more reasonable explanation.

Briefly the theory (elaborated in my papers[2–4]) is this. The fertilised ovum is a pan-potential cell. Its progeny soon differentiate into those whose descendants are to become gametes and into those which will produce the somatic tissues. In the former, groups of cells are constantly being set aside to nourish or protect the forerunners of the gametes—in other words, are being turned into soma cells. Cells are thus sacrificed in order that the eventual sex cells, after reducing divisions, may set free gametes under the best of conditions to perpetuate the species. I think it is reasonable to assume that cells thus discarded, on the eve as it were of being actual sex cells, will retain their capacity to form sex cells, even though this expression may be suppressed for the good of the individual as a whole. But these cells have become soma cells and the logical inference must be that latent in all the soma cells is this gametogenic capacity. The biological endeavour of every cell is to perpetuate its kind. When the somatic forces wane from countless cell divisions and old age, when nocuous factors such as X rays play upon groups of cells, when carcinogens make their life almost intolerable, is it not reasonable to assume that the latent gametogenic element in the nucleus, so long repressed for the good of the individual, may reassert itself

1. *Arch. path. Inst. Lond. Hosp.* 1906, **1**, 59.
2. Cleland, J. B. Some Remarks on the Causes of Cancer. *Aust. med. Gaz.* June 20, 1906, p. 279.
3. Cleland, J. B. Presidential address, section of pathology, Australasian Medical Congress. *Med. J. Aust.* April 12, 1924, supplement.
4. Cleland, J. B. Presidential address. *Roy. Soc. N.S. Wales*, 1918, **52**, 82.

with the production of a bizarre tissue, hopeless from the point of view of producing functional sex cells and moreover a tissue for which no adequate control has been provided in the body.

University of Adelaide. J. B. CLELAND.

HYDROCHLOROTHIAZIDE AND POTASSIUM EXCRETION

SIR,—The leading article on chlorothiazide (April 11) gives a clear and comprehensive account of its value as an orally effective diuretic and hypotensive agent.

In the final paragraph reference is made to 3,4-dihydrochlorothiazide and to the fact that its diuretic action is 10–20 times more potent than chlorothiazide. However, on the aspect of qualitative differences you comment that it is too early to say whether there is any less likelihood of excessive potassium loss than with chlorothiazide, and that present evidence suggests that this is not so.

I should like to draw attention to some recent publications which indicate that in regard to potassium loss there is a qualitative difference between the two substances.

Richterich et al., summarising their clinical experience with hydrochlorothiazide, state that "The natriuretic potency of hydrochlorothiazide is about 20 times that of chlorothiazide, while its effect on potassium excretion is negligible . . . the danger of hypotassemia is considerably less with hydrochlorothiazide than with chlorothiazide".[1] In a clinical pharmacological study Richterich writes: "Potassium excretion is (in contrast to chlorothiazide) not or only very slightly enhanced . . . The rise in bicarbonate and potassium excretion and the increase in urinary pH observed after chlorothiazide does not occur after hydrochlorothiazide".[2] Ford, dealing with urinary electrolyte excretion, says "The urinary loss of potassium and bicarbonate following this drug is relatively less than that seen with chlorothiazide. This has clinical implications in that the problem of hypokalemia will be much less".[3]

Ciba Laboratories Ltd., Horsham, Sussex. A. K. PITTMAN
Head of Medical Research Department.

LIVER BLOOD-FLOW

SIR,—May we express our appreciation of your report (Feb. 28) of the liver symposium held at Ibadan on Feb. 13–14? With reference to the description of the paper on liver blood-flow regulation there are, however, one or two points which, in the interests of accuracy, we feel should be corrected.

In the first place adrenaline does have a marked, though admittedly transitory, effect on liver blood-flow. Although it has a direct vasoconstrictor action on liver vessels, it raises liver blood-flow, partly due to the mechanical effect of raised blood-pressure, partly due to a reflex mediated through the baroreceptors and the vagal vasodilator nerves.[4]

That the action is transient is due to the effect of an overriding blood-flow control mechanism—namely, "intrinsic regulation". This phenomenon was first described under the name "autoregulation" with reference to the kidney.[5] It is also present in liver and brain; through its action the liver maintains a steady blood-flow even in the presence of large changes in blood-pressure.

To illustrate this phenomenon, lowering the blood-pressure from 160 to 60 mm. Hg produces a profound drop in blood-flow through the portal vein,[6] yet there is little change in liver blood-flow. The mechanics of this remarkable phenomenon involve both the spleen and the hepatic artery.[6] The spleen acts as an arteriovenous anastomosis opening up as the portal inflow from the bowel declines. The main compensation, however, is through the hepatic artery, which, at normotensive levels, supplies only about 30% of the liver's total blood, whereas at blood-pressure levels of about 60 mm. Hg it accounts for about 70% of the total. Below this level of pressure, the hepatic arterial contribution falls until at pressures of about 30 to 20 mm. Hg it ceases altogether, the only blood-supply remaining to the liver being a small contribution from the portal vein.

We have estimated hepatic resistance to arterial and to portal inflow. From experiments reported elsewhere we have concluded that the hepatic artery is a main controller of resistance to portal inflow, through its action on intrasinusoidal pressure.[7] Thus, the higher the hepatic arterial inflow, the greater is likely to be the intrasinusoidal pressure and the greater the resistance to portal inflow.

In a brief note such as this I should not like to speculate further except to state that we cannot accept that intrinsic regulation is entirely mechanical. It is not seen, for example, in tissues such as skin and bowel which are also well endowed with vascular smooth muscle. Nor is it seen in the isolated rat liver. This is the reason we have preferred the term "intrinsic regulation" to the term "autoregulation" as applied to the kidney.

One further point of correction which I feel should be made is that ligation of the hepatic artery produces an immediate fall in liver blood-flow (about 30%) followed by a slow but almost complete recovery (the recovery being an increased portal flow, due, we think, to a lowering of sinusoidal pressure). Ligation of the portal vein produces a marked fall in hepatic flow with no significant recovery.[7]

University College, Ibadan, Nigeria. J. GRAYSON
D. MENDEL.

GLUCOSE, SUCROSE, AND FRUCTOSE

SIR,—In their paper of March 7 Sir Charles Dodds and his colleagues have helped considerably to put certain controversial matters into proper perspective, and have at the same time emphasised the need for much further work in this field.

During the past three years we have carried out at this unit many similar observations to those of Dodds et al., and can confirm their findings with dextrose and sucrose.

Doses of 50 g. sugar have been used, the test subjects being laboratory workers fasted overnight. Despite considerable variation between individuals, and in the same person tested at different times, the results are essentially similar to those reported in tables I and II of Dodds et al. The only—and quite minor—discrepancy is that the fall below pre-dosing level of blood-sugar 90 minutes after the test dose appears to be less after sucrose than after dextrose in a higher proportion of our subjects.

Our observations have been extended to include a number of other sugars besides dextrose and sucrose, and the results to date indicate that there is a need for much more information than that cited by the Food Standards Committee in the appendix to its report.[8] Among the findings of other workers that we can corroborate is the difference between the blood-sugar curves following test doses of sucrose and of invert sugar, as reported by Albanese et al.[9] Rat studies, with techniques based upon those of Cori,[10] similarly indicate differences between these two materials, and confirm the glycogenic properties of fructose that he described.

The metabolic differences between these sugars are being investigated further, with particular reference to fructose and to other non-glucose-reducing substances in the blood following test doses, and will be published in due course.

1. Richterich, R., et al. *Schweiz. med. Wschr.* 1959, **89**, 353.
2. Richterich, R. *Klin. Wschr.* 1959, **7**, 355.
3. Ford, R. V. *Sth. med. J.* 1959, **52**, 40.
4. Grayson, J., Johnson, D. H. *J. Physiol.* 1953, **120**, 73.
5. Shipley, R. E., Study, R. S. *Amer. J. Physiol.* 1951, **167**, 676.
6. Ginsberg, H., Grayson, J. *J. Physiol.* 1954, **123**, 574.
7. Grayson, J., Mendel, D. *ibid.* 1957, **136**, 60.
8. Ministry of Agriculture, Fisheries, and Food. Food Standards Committee: Report on Soft Drinks. H.M. Stationery Office, 1959.
9. Albanese, A. A., Higgons, R. A., Orto, L., Belmont, A., Di Lallo, R. *Metabolism*, 1954, **3**, 154.
10. Cori, C. F. *J. biol. Chem.* 1926, **70**, 577.

Dr. Allen (March 28) requests evidence relating to the better utilisation of fructose than of dextrose by persons other than diabetics: this matter was discussed, with available evidence, in the paper by Albanese et al., as was the utilisation of fructose by muscle, liver, kidney, and lung tissue without prior transformation to glucose or glycogen. The belief that fructose is unavailable for utilisation by the peripheral tissues without such conversion [11] appears to be incorrect, as will be discussed in detail in our forthcoming publication.

Nutritional Research Unit, Huntingdon. ALASTAIR N. WORDEN.

PRISON MEDICAL OFFICERS

SIR,—"White Slave" (April 4) contends that prison medical officers are unable to gain adequate psychiatric knowledge; and "Consultant Psychiatrist" (April 11) sneers because they have no such knowledge. Yet I know of three doctors who have left the Prison Medical Service during the past few years and now practise consultant psychiatry, while a fourth applied for and was offered a senior post at a mental hospital, but declined it finally on the grounds that the accommodation offered did not permit the keeping of his dog. This medical officer is still serving. Those who have obtained high qualifications appear to lose no opportunity of quitting the service.

Similarly, efforts to recruit into the service psychiatrists of registrar status appear to have been abortive, since the salary scales and the professional status have proved inadequate, and in spite of the fact that it has been authorised for some years that such suitably qualified and experienced medical officers will commence on a higher salary within the approved scale.

"Consultant Psychiatrist" wishes all the appointments to the East-Hubert Institution and to the proposed Remand Centres to be made from existing National Health Service specialists, in spite of the fact that they may have no special knowledge of *forensic* psychiatry.

"White Slave" simply complains that no prison medical officer will be well enough qualified to be considered for such a post; but the Prison Commissioners clearly wish to have both types appointed.

In the meantime, the attack on prison medical officers, and disdain for their frustrations and ambitions, do not seem to be helpful.

STULTUS.

ANTIBIOTIC COMBINATIONS

SIR,—We present here the preliminary findings in a clinical trial conducted by ten general practitioners in Bradford.

Certain combinations of two antibiotics have been found to have a more powerful antibacterial action than their components singly,[12] and it has been suggested that such combinations can at least delay the emergence of resistant strains.[13] It was decided, therefore, to attempt to discover whether a combination of novobiocin and tetracycline ('Albamycin-T', containing 125 mg. novobiocin and 125 mg. tetracycline hydrochloride per tablet) had any apparent advantages clinically over novobiocin ('Albamycin' 250 mg. per tablet) and tetracycline ('Achromycin-V' 250 mg. per tablet) alone. The use of novobiocin and tetracycline alone or in combination for all these cases does not imply that they would necessarily have been chosen in other circumstances.

The patients chosen had soft-tissue, ear, nose and throat, and intrathoracic infections. The daily dosage of the antibiotics was based on the adult dose of 1 g. novobiocin, 1 g. tetracycline, or 1 g. of the combination (500 mg. novobiocin and 500 mg. tetracycline), and the response to treatment was graded as rapid, slow, or nil. Five of the investigators compared novobiocin with the combination, and five compared tetracycline with the combination.

All the observations were purely clinical since it was felt that the conditions of the trial should be those under which antibiotics are commonly employed in general practice: there was no bacteriological control.

The results of treatment in 281 cases have been collected:

	Response		
	Rapid	*Slow*	*Nil*
Novobiocin	48 (*63%*)	19 (*25%*)	9 (*12%*)
Tetracycline	48 (*58%*)	29 (*35%*)	6 (*7%*)
Novobiocin/ tetracycline	109 (*90%*)	12 (*9%*)	1 (*1%*)

These results suggest that the combination may be considerably more effective than either antibiotic singly, for the impression was gained that a satisfactory response was obtained more rapidly with the combination. The study is being continued in order to build up a large series, and it will be reported in full later.

F. J. BIRKETT — F. A. BREAR
J. BRECKENRIDGE — R. HIGH
R. A. MCGREGOR — M. MCK. SHAW
S. A. PRICE — J. P. SHACKLETON
I. J. WAITE — A. J. WALEWSKI.

THE WORTHING VERSION

SIR,—In your annotation of March 28 you say that "The figures which Dr. Carse offers seem to withstand critical scrutiny." We pointed out in a letter last year [1] that the first report [2] of the Worthing experiment showed that the admission-rate to Graylingwell Hospital in 1957 had been reduced to a level almost equal to that of national expectation. The admission-rate in 1956, taken as a comparable baseline for the experiment, was almost two-and-a-half times greater than for the country as a whole. This criticism was not answered at the time and there is no reference to it in the more recent report to the South West Metropolitan Regional Hospital Board, which is the subject of the present annotation. It was, perhaps, to be expected that the vigorous use of external services would, in the circumstances, produce a fall in the admission-rate from the catchment area. This in no way detracts from the local value of what is being done; but the figures do not necessarily imply that in other places, especially those which have had fairly well-developed external services for some time, and in which the annual admission-rates are no greater than national expectation, a further substantial reduction could be achieved.

Although the report emphasises the importance of the admission-rate, it may be thought that this is not the only, or indeed the most appropriate, criterion to use. For example, one patient in residence for three months means more "inpatient days" than the same patient admitted for three periods of a fortnight each. There is a brief reference to "inpatient days" in the report, but we wonder why more use has not been made of this illuminating kind of information in assessing results. It appears that about three-quarters of the reduction in admissions is accounted for in respect of admissions to the non-statutory part of Graylingwell, Summersdale. It would be enlightening to know more about the impact which may have been made on the hard core of the more intractable cases. Does it accumulate any less rapidly than it used to do? And if so, is this due to the expansion of external services alone or do new methods of physical treatment also contribute? In 1957, the numbers of patients in residence in the mental hospitals of the country as a whole fell for the first time for a great many years.

To reduce the numbers of patients in residence in any large

11. Douthwaite, A. H. *Practitioner*, 1959, **182**, 482.
12. Furesz, S., Zangaglia, O., Scotti, R. *Antibiot. Chemother.* 1958, **8**, 571.
13. Lin, F.-K., Coriell, L. L. *Antibiot. Med.* 1957, **4**, 35.

1. *Lancet*, 1958, i, 319.
2. *ibid.* p. 39.

mental hospital by 100 or more from one year to the next, as is mentioned in the report, is an achievement. To what extent was the reduction in the numbers resident in Graylingwell brought about by successfully treating early cases which would otherwise have become chronic and to what extent by discharging stabilised long-stay patients? If the latter element was substantial, where are the patients now? How many are in their own homes, how many in other "homes", and how many in part-III accommodation under their local authorities? Informal reports from other places where active extramural rehabilitation of chronic patients has been pursued suggest that it is one thing to get them out of hospital, but quite another to keep them out of any kind of institutional accommodation. We feel that the answers to these questions, which may well be favourable in an area where social conditions appear to be good, would enable other observers to form a clearer assessment of the value of the experiment than they can at present.

Finally, since you quote fairly fully from the concluding discussion in the report, may we correct one possibly misleading suggestion that it contains—namely, that "for the past twenty or thirty years outside London and one or two of our largest cities . . . treatment meant that the patient must be in hospital". According to the Feversham report,[3] there were at least 166 psychiatric outpatient clinics or centres in England and Wales as long ago as 1936. And the concept of an external mental health service—including domiciliary visiting—rather than one of mere mental hospital administration, was in action before the war; it has been described in a monograph by Shepherd.[4]

Our purpose in writing is to ensure that these sensible steps which started many years ago, and of which the Worthing Version is an up-to-date example, are not prejudiced by the selection of startling statistics which might give an excessively sanguine expectation of the general prospects ahead in the country as a whole.

The Warneford Hospital, Oxford. R. W. PARNELL
IAN SKOTTOWE.

MENTAL HEALTH BILL

SIR,—In an effort to give consultant psychiatrists in mental hospitals full responsibility for their patients, correspondence on the Mental Health Bill has tended to concentrate understandably on proposals for modifying the role of the medical superintendent in the administration of the hospital. Whilst I am in full agreement with such discussions, I would like to suggest that there is a complementary aspect to this problem which deserves attention—the building-up of comprehensive psychiatric departments in general hospitals.

The Manchester region has, I think, taken the lead in sponsoring departments in general hospitals which deal with the whole range of psychiatric problems. My own inpatient department, for example, is coping with a growing majority of the patients from a population of some 254,000. As a result of structural upgrading, half of the department is at present closed, but when fully open in the near future, it will have a complement of 122 beds. It is anticipated that in due course the department will cope with the bulk of the psychiatric patients from the catchment area who require inpatient treatment. Cases are admitted under legal orders, in addition to voluntary and informal admissions. There is no medical superintendent. There is a lay superintendent who is the administrator of the whole hospital, but it is taken for granted that the consultant in charge of the psychiatric department makes all the relevant medical-administrative decisions concerning his patients. (In passing, it should be stated that this type of department, being situated in the centre of a densely populated urban area, conduces to close liaison with local authorities, general practitioners, social workers, and others, and leads logically to the building up of a "district mental health service".) I would say, therefore, that the provision of comprehensive psychiatric departments based on general hospitals is one of the most constructive ways of ensuring clinical independence for the psychiatric consultant.

It seems appropriate to point out that I am also on the staff of a large mental hospital being, in fact, chairman of its medical advisory committee. I regard the psychiatric department in the general hospital and the large mental hospital as different parts of one mental health service.

Department of Psychological Medicine, Queen's Park Hospital, Blackburn, Lancs. MAURICE SILVERMAN.

SIR,—I should like to clarify the point I tried to make in my letter of Feb. 28 about the Royal Medico-Psychological Association, which drew criticism from Dr. Monro (March 14).

In this country legislative action is usually a matter of compromise. Specialist organisations present their views to Royal Commissions which modify these views somewhat in their reports. Subsequently, Parliament, representing the electorate, modifies these proposals even further before making them Law. One need only cite the recent example of the report on homosexuality and prostitution to indicate a somewhat extreme form of the common pattern. Paradoxically the progress of the current mental-health legislation has been quite the reverse of this. The Royal Commission expanded and improved on the R.M.P.A.'s proposals and the Government has improved even further on the Royal Commission report. (Is it too much to hope that this pattern may be maintained with the Royal Commission on medical remuneration?)

I feel that there is a moral in this for the R.M.P.A in spite of all the conscientious and laudable industry shown recently by Dr. Monro and his committee. Since medical administration in mental hospitals is a current problem, could not a research organisation be constituted in collaboration with the King's Fund to investigate this matter further?

Alternatively this might be an opportunity for the R.M.P.A to put its own house in order. Its constitution probably served well in 1926 when its charter was granted, but it is difficult to see how the R.M.P.A can claim to represent psychiatric specialists today. Physician-superintendents, active or retired, account for only 14% of the membership of the Association, but they account for between 60% and 80% of the membership of the council and its associated committees, which are selected rather than elected. It is apparent that it must be difficult for them to express views at variance with their own as the official view of the R.M.P.A. Dr. Monro has done well to persuade them to recognise consultants as "responsible medical officers", but it should not be forgotten that it has taken 2 years for this to be achieved.

It is heartening to learn that the Minister of Health recognises that the correspondence columns of your journal display points of view which differ from those of the R.M.P.A. but one would wish that it need not be so.

Cane Hill Hospital, Coulsdon, Surrey. JOHN T. HUTCHINSON.

SIR,—I hope the Minister of Health will not be persuaded to implement the extraordinary scheme of appointing medical superintendents (or "directors") suggested by Dr. Beckett (April 11). If an atmosphere of hustings is introduced into hospitals, we shall soon be having all the paraphernalia of nomination procedures, registration of proper electoral rolls, polling-booths, and a series of meetings addressed by half a dozen or more consultants and senior hospital medical officers who will explain how and why they can best direct a hospital. In any case, it is very doubtful whether the scheme outlined is either practicable or desirable.

Dr. Beckett considers that there should be weighting of

3. The Voluntary Mental Health Services: Feversham Committee; p. 60. London, 1939.
4. Shepherd, M. A Study of the Major Psychoses in an English County; p. 18. Maudsley Monographs No. 3. London 1957.

doctors and nurses over clerks and artisans, though he does not indicate arithmetically whether a doctor's vote should be worth twice, thrice, or six times that of an artisan. But can any weighting scale be truly democratic? If a hospital is administered as a therapeutic community, each worker has his or her specific role to play which fits into a complete pattern, and from this point of view all are of equal and necessary importance: those who arrange for the supply of adequate food, the kitchen staff who prepare meals, the artisans who maintain the standard of heating and lighting, the doctors who carry out psychotherapy or other treatments, the nurses who soothe and comfort the patients in their fears and anxieties, the garden workers who supply vegetables, and so forth, and so on; and the staff of *all* departments inasmuch as they help in the occupational therapy of patients. And has not a rather important section of the possible electorate been forgotten—the patients? After all, the hospital is organised primarily for the benefit of patients, and a large percentage of them are quite capable of passing a fairly reasonable judgment. Are they not to have any say in the matter?

Finally, if we are to pursue this logic of "democratic" appointments, should it not be applied also to such officers as secretary-superintendents, consultants, group secretaries, matrons, chief male nurses, and superintendent engineers, of whom a number have been accused by somebody or other, at one time or another, of being dictatorial, unprogressive, or lacking in good interpersonal relationships. Perhaps such officers could also be stimulated to improve themselves if their appointments depended on a re-election by "democratic" vote every three or five years. Should an officer fail to be re-elected, he could be transferred on an exchange basis to another hospital where a similar event has occurred; it might well turn out, as so often happens with members of Parliament who change constituencies, that both will find better favour with their new electorates.

Park Prewett Hospital, Basingstoke. I. ATKIN
Physician-superintendent.

Dr. H. DALE BECKETT writes:

"The meaning of my letter in last week's issue was unfortunately quite altered by a misprint in the last paragraph. It would be a 'vigorous', rather than a 'rigorous', medical administration which would result from the changes I outlined."

THE BUDGET

SIR,—In the past, *The Lancet* has maintained a high standard as a medical and scientific weekly journal eschewing controversial party-political topics. Many of your subscribers will have been distressed, as I was, to read your annotation last week on the Budget. A comment, Sir, which might well have come from the pen of Mr. Harold Wilson, the next Socialist Government's Chancellor of the Exchequer.

It is to be hoped that *The Lancet* will confine its activities to medical and scientific subjects.

W. FERGUSSON HANNAY.

***We fully agree with Sir Walter about eschewing party politics; but *The Lancet* has always been, and still is, concerned with social as well as medical advance. We are so anxious to see more money spent on social improvements—better prisons, better medicine, better education, and better subsistence levels—that our reaction to the Budget was admittedly one of disappointment. But we are of course well aware that such improvements depend in the long run on national prosperity, which the Budget is designed to promote. We do not pretend to know whether its initial disappointments will prove unimportant compared with its eventual social benefits; and we shall be very glad if they do.—ED. L.

Parliament

Crime and Penal Practice

THE number of indictable offences is higher today than it has ever been before, and it is roughly twice as high as before the war. As the provisional figures for 1958 show (see below), we still do not seem to have reached the peak of this disquieting wave of crime. In opening the debate in the House of Lords on April 8, Lord PAKENHAM could find comfort only in the comparatively good record of the post-war generation of children, now in the 8–11 age-group. On the other hand, the generation born during the war years have at all stages of their lives done more than their share of crime and have made an unhappy contribution to the figures for 1958.

Lord Pakenham wondered whether this level of crime was so surprising when it was remembered how pathetically little we had been spending on research into criminology and that the national arrangements for dealing with delinquents since the war had been allowed to lag far behind the other social services. Our probation officers were underpaid and unrecognised. We had seriously undernourished our prison services. We had shamefully starved the aftercare services for released prisoners. We were willing to spend money on defence for our physical preservation. The battle against crime was for our moral preservation. Yet even this year, which was to be one of unprecedented expansion, we were to spend only £14½ million on prisons and £182,000 on aftercare. In short we were trying to deal with criminals on the cheap. He admitted that whatever the causes of crime, and we were sadly ignorant about them, the immediate cause of the lamentable position in our prisons was the increase of crime. The growing number of prisoners had caught up and indeed overtaken the efforts of the authorities, and overcrowding and understaffing were now worse than two years ago. In penal reform we had at least always recognised our responsibility, however feebly and gropingly we had moved towards it. But in aftercare we had not even recognised our responsibility, and he feared that a revolution in our outlook would be necessary before we did so.

Viscount TEMPLEWOOD pointed out that we used to think that poverty was the main cause of crime—bad living conditions, bad housing, and inadequate education. Since the war we had seen a great rise in material wealth, and a great increase in the social services, yet we had seen crime steadily rising even to a greater extent. In his view that was a formidable problem. Lord MOYNIHAN too was uneasy about the effects of the Welfare State. Excellent in theory, was it not, he asked, in practice turning out to be an ill-timed attempt to alleviate the fears and increase the happiness of the masses? Because of the speed with which it had been presented it was encouraging people to work less for more money and without any positive idea how to use their spare time. But though he thought some welfare services had been expanded too quickly, he clearly did not hold that view about our prison service. In building, he pointed out, we had lagged far behind every other country. We always said that money was short, but after the Budget he did not believe that anyone could say that we were living in a time of financial stringency and the conditions in our prisons should no longer be tolerated.

Lord NATHAN made an important contribution to the debate when, as its chairman, he announced that the Isaac Wolfson Foundation was to give £150,000 to the University of Cambridge to found a chair and a readership in criminology and perhaps a library at the institute of criminology which it is proposed to set up there.[1]

Viscount KILMUIR, the Lord Chancellor, held that the increase in crime was the responsibility of society as a whole and could not be solved by administrative or legislative measures alone. He was disturbed not so much by the periodic steep increases in crime as by the fact that the ground lost during the war had never been recovered. He was also disquieted by the persistent increase in crimes of violence and in sexual offences, though he was glad to say that the figures for 1958 almost for

1. See *Lancet*, Jan. 3, 1959, p. 34.

the first time since the war showed a decrease in this last group. We must not forget, moreover, that offences of violence and sexual offences account for only 30,000 out of well over half a million crimes known to the police. Of the crimes of violence only 9% were associated with robbery and other serious incidents. What we had to face was that the bulk of crime consisted of offences of dishonesty. He stressed that the Government's prison-building programme was not merely a paper programme. Work would begin at seven sites during this year and the Government was anxious to see the whole programme under way as fast as was reasonably possible.

Lord SILKIN welcomed the new institute, for until we knew more about the causes of crime we were dealing only with the symptoms and not the disease and committing ourselves to remedies before we had found out what the real problem was. He agreed that it would not be possible to get results quickly, but he suggested that statistics could be more reliable and could be provided earlier. The present returns, for example, did not discriminate between a trivial and a serious assault. Their interpretation varied from police district to police district and so they were not strictly comparable. Above all they gave no information about recidivism. He hoped that the new institute would give us a really accurate and reliable measure of the success or failure of different forms of treatment.

Baroness WOOTTON OF ABINGER, speaking as a magistrate, was also anxious for this kind of help. By and large doctors found out whether their patients died or got better, teachers found out whether their pupils passed their examinations or failed, but judges and magistrates had no organised follow-up. In their present form statistics did not tell whether the increase of crime was due to greater activity by established criminals or a spread of criminal habits. She also, slightly apologetically, called attention to the extraordinary discrepancy between the crime-rates of the male sex and the female. At the peak ages about eleven times more offences were committed by boys than girls. She thought that this raised doubts about some current rather easy explanations. Girls had the same indifferent neglectful parents and were exposed to the same risks of broken homes.

Lord TAYLOR, considering what psychiatry had had to contribute to the study of crime, said that conventional mental disease was not an important factor in the cause of crime. Criminality, in so far as it was a problem of psychiatry, was largely a problem of the psychopaths, the group for which at present psychiatrists could do least. Psychopathy was not easy to define but it appeared to be the bad features of a normal personality written in capital letters and deprived of the compensating features. Normal people grew out of these bad features, but the psychopath did not. He lacked the capacity to learn from experience or from any kind of teaching device society was able to devise. Lord Taylor therefore believed that the first task which research on crime should tackle was to obtain a proper natural history of psychopathy. The other important problem was the efficacy of different methods of treatment. Social research of this kind was expensive and the money we were spending on research in relation to the total cost of the prison service was very small. He hoped that the Government would spend really generously on this work.

Lord STONHAM suggested that overcrowding in our prisons was largely due to wrong classification of the inmates. The result was not only a waste of public money but meagre results in the rehabilitation of offenders. We should remove from our ordinary prisons the human derelicts, geriatrics, and misfits, who were enemies not of society but of themselves. They cluttered up the prisons and impeded officers in the task of rehabilitating those who had committed serious crimes. On conviction they should be classified by doctors and probation officers and if necessary they should be detained in a colony under ordinary discipline and obliged so far as possible to earn their keep. If we could classify offenders, train them according to their abilities, and on release see that they went to jobs for which they had been trained he was sure that our prison population would shrink to a size well within the capacity of the present prison service.

In the closing speech for the Government Lord CHESHAM, reviewing the problem of juvenile delinquency, said that a generation normally produced its peak of delinquency at the age of 14. The present generation had produced a further peak at 17. Since the war juvenile delinquency had fluctuated, but 1957 was the worst year. The only comfort was that children now under the age of 14 had so far a better record than their predecessors who were now causing so much anxiety as young adults. But we should be cautious in accepting statistics as the true measure of delinquency, especially when comparing pre-war and post-war figures. Statistics reflected changes in custom for which we could not allow. For instance he was sure that offences by children were now more readily reported to the police and that the police were probably more ready to bring them before a juvenile court. The Government had no wish to underestimate the seriousness of the situation and he agreed that it was for the Government to punish crime. But the Government had only a limited part to play in dealing with its cause. Perhaps we were only beginning to realise how limited a part. We used to think that poverty, bad housing, and inadequate educational and social services were the main underlying causes of crime. They must be contributory, but it was clear that they were not the whole story. More recently we had assumed that war-time experience had played a part. But even among the post-war children delinquency had continued to rise, and it seemed reasonable to assume that the causes of juvenile crime were more deeply rooted than we once thought. He believed that they were so deeply rooted as to be largely beyond the reach of Government action. To cure crime would require a gigantic operation by both central and local government, by the Churches, by the voluntary societies, and by an increase in the moral responsibility of the people as individuals.

QUESTION TIME

Fallout

Mr. REGINALD MOSS asked the Prime Minister, in view of the fact that the rate of accumulation of strontium 90 was twice as rapid as was previously supposed, and that the residence half-life of radioactive material in the atmosphere was shorter than was previously believed, if he would give an estimate of the consequences these facts had for the health and welfare of individuals and of the general population of the country.—Mr. HAROLD MACMILLAN replied: The latest American theories about the rate of fallout are being studied, and I am not yet in a position to make a statement. We have, of course, a comprehensive monitoring programme in this country. The Medical Research Council has recommended that immediate consideration would be required if the concentration of strontium 90 in human bones showed signs of rising greatly beyond ten strontium units. The latest measurements do not indicate that we are approaching anywhere near this level.

Mr. ROY MASON: In view of the fact that the Russian dirty tests and the American high-level tests took place many months ago, and as it has been admitted that we already have a good tracking system, is it not a fact that the Atomic Energy Authority's recordings have already confirmed the American statements that strontium 90 has more than doubled in the atmosphere and is gradually falling in this belt? Mr. MACMILLAN: Undoubtedly, it has increased, but it is nowhere near the danger level yet. Nevertheless, it makes it all the more important to try to bring these negotiations to a satisfactory conclusion.

Radioactive Waste

At present there are no regulations governing the disposal of waste. An expert panel of the Radioactive Substances Advisory Committee has reported on the best way to control its handling and disposal, and the Government will shortly be consulting the local-authority associations and others interested about proposals for legislation and the issue of a white-paper will then be considered. In the meantime the Atomic Energy Authority are willing, as an interim measure, to help in the disposal of radioactive waste which cannot safely be disposed of locally.

Cost of Drugs for Private Patients

The estimated cost of providing free drugs and dressings to the 3% of the population of England and Wales not using the National Health Service general medical service would be nearly £2¼ million. This estimate necessarily depends on certain assumptions.

Criminal Statistics

The number of indictable offences provisionally recorded in 1958 up to Sept. 30 was 458,162, an increase of 14·7% compared with the corresponding period in 1957. This included 95,890 breaking and entering offences, an increase of 26% over the previous year. The number of offences of larceny increased by 13% to 298,369. The increase in offences of violence against the person was 9% and there was a decrease of 10% in sexual offences. Offences of robbery increased by 38% to 1157. The total number of persons found guilty of indictable offences increased by 12·2%. The increase among young people aged seventeen to twenty-one was 26·7%, and among those aged fourteen to seventeen it was 17·5%.

Obituary

DEBABRATA CHATTERJEE

M.B. Calcutta

Dr. Chatterjee, a former senior house-officer in thoracic surgery at Grove Park Hospital, London, died on April 1, at the age of 31.

He qualified from the Medical College, Calcutta, in 1953, and after holding house-appointments in his teaching hospital he decided in 1957 to specialise in general medicine and diseases of the chest. He came to this country to gain more experience, and worked at Grove Park Hospital as the house-surgeon in the thoracic surgery department and later as registrar on the medical side. He was taken ill in Edinburgh, where he had gone for further postgraduate study.

M. M. N. writes:

"Chatterjee will be remembered as a young man of charm, education, and honesty of thought and purpose. During his short time in this country he made many friends and was extremely well liked by his patients and colleagues, senior and junior. Even during his illness his mind was never at rest. He began to learn French, and discovered that he could work well with his hands, and began to develop several hobbies."

Appointments

ARDLEY, JOHN, M.B. Durh., D.P.H.: M.O.H., Blackburn.
ARKLE, ELIZABETH, M.D. Bratislava, D.P.M.: part-time consultant children's psychiatrist, Mapperley Hospital, Nottingham, and child-guidance centres.
BRAY, CYNTHIA A. R., M.B. Birm., D.OBST., D.C.H.: assistant M.O.H. and school M.O., West Bromwich.
FRASER, I. G. P., M.B. Edin., D.P.H.: senior assistant M.O., Nottingham.
MACFARLANE, J. C. W., M.D., B.SC. Glasg.: clinical pathologist, London Chest Hospital.
MOSS, B. J. L., M.B. Lond., D.C.H., D.P.H.: deputy M.O.H. and deputy principal school M.O., Leicester.
POVER, N. T. W., L.R.C.S.E., D.P.H.: district M.O.H., Thetford, Swaffham, and Wayland, Norfolk.
ROADS, P. G., M.D. Lond., D.P.H.: M.O.H. and principal school M.O., Portsmouth.
STORY, DORIS, M.B. Durh., D.P.H.: assistant M.O., Nottingham.
VEREL, DAVID, M.D. Cantab., M.R.C.P.: consultant cardiologist in charge of regional cardiological centre, City General Hospital, Sheffield.

The Hospital for Sick Children, Great Ormond Street, London:

COTTON, D. A., M.B. N.Z.: house-physician.
COURTEMANCHE, A. D., M.D. Toronto: house-surgeon, orthopædic and plastic departments.
DEOBHAKTA, ZARINA A., M.B.: R.M.O., Tadworth Court.
NICHOLLS, MONTAGUE, M.B. Manc.: assistant R.M.O., Tadworth Court.

London Hospital:

COUCH, R. S. C., M.D. Lond., M.R.C.P., F.F.R., D.M.R.D.: consultant radiologist.
MASON, A. STUART, M.D. Cantab., M.R.C.P., consultant endocrinologist.
WILKINSON, A. E., M.B. Lond.: consultant pathologist, venereal diseases reference laboratory.

Notes and News

HOSPITAL DIET

"GOOD food, well cooked and attractively served, is an important part of treatment and the catering department makes a big contribution towards the well-being and full recovery of everyone in the hospital." These are the opening words of the third memorandum on Hospital Diet[1] which is the latest contribution from King Edward's Hospital Fund for London.

Dr. Avery Jones, chairman of the Hospital Catering and Diet Committee, explains in his foreword that the views expressed are based on the experience gained by the King's Fund Hospital Catering Advisory Service and School of Catering during the first decade of the National Health Service. He regards as the outstanding current problem in many hospitals the structural inadequacy of kitchens, which are not only poorly equipped but also badly designed. Linked with this, but more serious, is the problem of staff shortage.

Because many general hospitals provide a complete medical service, the memorandum points out, the catering department has to feed not only patients in the medical and surgical wards but also those in the maternity, tuberculosis, pædiatric, and geriatric units. Although these patients have different needs they can be met in practice by an intelligent modification of normal meals.

There are often particular catering problems in mental hospitals, with a thousand or more beds, because of the large number of meals required at the same time, and the difficulties of cooking and distributing the food in old and scattered buildings. The King's Fund suggests that decentralisation by establishing two or three kitchens, and the provision of a central diningroom for selected ambulant patients, would help to raise the standard. The food itself should be nutritionally adequate, especially in respect of animal protein and vitamin C, and minimum quantities of various foods are suggested.

Good food and proper service are important also in keeping hospital staff content, and the memorandum suggests that nurses (who have seen and served the food on the wards) should have a different menu from the patients. If this is not possible there should at least be a choice of dishes at each meal. Probably the best way of achieving this is to provide the staff with a cafeteria service in a common diningroom. For those on night duty meals should be freshly cooked, and whenever possible they should be eaten away from the wards.

Improvements in the standard of hospital catering depend largely on the efficiency of catering officers. The duties, qualifications, and training of hospital catering officers and dietitians are described, and the King's Fund puts forward the proposal that senior catering officers in the larger hospitals (i.e., those providing more than 500–600 midday meals) should be given the designation of "catering manager". In general hospitals the assistance of a dietitian is necessary in order that therapeutic diets and certain diagnostic tests shall be accurately carried out. The dietitian should also exert her influence as a "nutritionist and teacher" on the hospital as a whole.

In other chapters the factors affecting food costs and the siting of the main kitchen, and the importance of hygiene in hospital catering departments, are discussed.

DOCTORS' WINDOW IN GUILDFORD CATHEDRAL

THE medical profession is one of the groups which have promised to give a window to Guildford's new cathedral, and Miss Moira Forsyth has been asked to design the doctors' window, which is to be in the nave.

Each window, of which there are seven along the south side, consists of a double lancet mainly of handmade clear glass, but at the bottom of each lancet is a coloured panel. Miss Forsyth has depicted two scenes connected with healing, one from the Old Testament and one from the New—Moses setting up the serpent of brass upon a standard, and the raising of Jairus' daughter.

1. Third Memorandum on Hospital Diet, April, 1959. Copies may be had from King Edward's Hospital Fund for London, 34, King Street, London, E.C.2. Pp. 63. 2s. (post free).

Contributions to the doctors' cathedral window fund have so far reached over £800, which is more than half the amount which it is hoped to raise. But further contributions are urgently invited and should be sent to the secretary of the fund, Dr. F. A. Belam, 1, Westfield, Epsom Road, Guildford, Surrey, as soon as possible.

NEW FLAMMABILITY STANDARDS

AN important advance in the campaign against accidents in the home and factory is the publication of new British Standards for "flame resistance" of clothing.[1]

Flame resistance is defined as the time in seconds for a flame to travel vertically 100 inches up a fabric. B.S. 3121 proposes that clothes should have a rating of at least 150, and that this should be retained after twelve intensive washings, each consisting of half an hour's treatment with concentrated chemicals and detergents in a washing-machine. This drastic treatment is to ensure that fabrics that are proofed by chemical treatment will retain their resistance after washing.

These standards have been adopted by the Board of Trade and new regulations, under the Fabrics (Misdescription) Act, 1913, will make it an offence to offer for sale fabrics claimed to be flameproof unless these comply with the standards. The regulations will come into force on May 11, 1959, and clothes marked with the B.S. 3121 label will be able to be relied on for protection from the ordinary burning accidents in the home.

GROWING OLD

IN a booklet entitled "Growing Old",[2] Dr. Thomas Rudd asks his readers to regard old age as a natural stage of life which has its own particular contribution to make to the community.

The problems of old age are the price we have to pay for our own chances of happy and healthy survival, and Dr. Rudd believes that we have no right as individuals to benefit from longer years of life if we are unwilling to take some responsibility for the care of other people in their old age. He points the way to a practical solution of these social debts.

HEIGHT AND WEIGHT CHARTS FOR BOYS AND GIRLS

HEIGHT and weight charts based on British standards have not been generally available in this country. Dr. P. E. Polani has now constructed such charts for the medical advisory committee of the National Spastics Society.

The charts are based on data obtained from the Oxford child health survey and the London County Council report on heights and weights of children in the county of London. Separate height and weight charts have been printed for boys and girls, and the age-range is from birth to 16 years. Height and weight graphs are shown separately, and represent the mean and values of 1 and 2 standard deviations above and below the mean. The legend on the back gives details of the construction of the charts, the significance of the curves, and the method of measuring the children.

The charts can be obtained from the medical research unit, National Spastics Society, Department of Child Health, Guy's Hospital, London, S.E.1 ($1\frac{1}{4}d.$ each, plus postage).

University of Birmingham

Prof. J. R. Squire has been appointed deputy dean of the faculty of medicine for 1959.

University of Glasgow

On June 17 the honorary degree of LL.D. will be conferred on Prof. Dugald Baird.

National University of Ireland

On April 16 the honorary degree of M.CH. was conferred on Prof. M. G. O'Malley.

Faculty of Radiologists

On Friday, May 8, at 4.30 P.M., at the Royal College of Surgeons of England, Lincoln's Fields, London, W.C.2, Dr. S. Cochrane Shanks will deliver the Knox lecture. He will speak on medicine, radiology, and the law.

1. B.S. 1547: 1959. Flameproof Industrial Clothing (Materials and Design); B.S. 3119 : 1959. Method of Test for Flameproof Materials; B.S. 3120: 1959. Performance Requirements of Materials for Flameproof Clothing; B.S. 3121: 1959. Performance Requirements of Fabrics Described as of Low Flammability. Price 3s. each. Obtainable from Sales Branch, British Standards Institute, 2, Park Street, London, W.1.
2. Copies may be had from the Catholic Truth Society, 38/40, Eccleston Square, London, S.W.1; S 245, price 4d.

Royal College of Surgeons of England

At a meeting of the council on April 9, with Sir James Paterson Ross, the president, in the chair, Prof. John McMichael and Mr. Douglas Robb were appointed Sir Arthur Sims Commonwealth travelling professors. Prof. C. G. Rob was admitted a member of the court of examiners. Mr. J. A. Shepherd was admitted to the fellowship (*ad eundem*).

The following were elected fellows of the college without examination as being medical practitioners of 20 years' standing:

Dr. A. H. Bennett, Dr. S. F. Logan Dahne, Sir Joseph Pierre (Trinidad), Dr. C. MacPherson (Newfoundland), Mr. A. T. Britten Jones (Adelaide), Prof. A. J. E. Cave.

Mr. L. E. C. Norbury was appointed Gordon-Watson lecturer and Dr. E. F. Scowen Imperial Cancer Research Fund lecturer for 1960. A Moynihan lectureship was awarded to Dr. Bradley Coley (New York) and a special lectureship to Dr. Barry Anson (Chicago). The council selected as the subject for the Jacksonian prize for 1960 the ætiology, investigation, and treatment of renal calculus.

Dr. Ashley Daly and Dr. H. R. Griffith were elected honorary fellows in the Faculty of Anæsthetists, and the following were elected fellows without examination:

Dr. R. H. P. Fitzpatrick, Dr. A. Goldblat (Brussels), Dr. T. Gordh (Stockholm), Dr. G. A. Haydock, Dr. E. Nilsson (Lund).

A diploma of fellowship in the Faculty was conferred on P. J. Armstrong (by examination).

A diploma of membership of the college was conferred on Gordon Taylor and the following diplomas were granted, jointly with the Royal College of Physicians:

D.P.H.—Mildred M. E. Barnard.

D.Phys. Med.—D. C. Beatty, J. B. Brennan, Neil Cardoe, A. C. Jayasuriya, Joyce J. P. Lomas, I. A. Williams.

D.M.R.T.—A. T. Abdel-Messieh, M. J. T. Adams, J. D. Bradshaw, J. M. Brindle, Irene M. S. Cade, P. J. Fitzpatrick, L. del Rosario Lopez, Vaidheeswaran Pasupati, G. R. Prager, W. J. K. Simpson, M. E. Tulloh.

D.M.R.D.—A. F. Barrett, C. J. Barton, J. B. Crowe, A. D. Gentle, P. W. Gilman, J. H. Gough, William Granger, W. B. James, H. I. Jory, B. E. Kendall, J. G. Kenney, D. R. Knapp, P. R. Kossick, Michael Lea Thomas, D. R. McDonald, Mala Maw, Rasheed Ahmad Mian, G. H. Moss, J. T. Paton, Hettiarachige Wijayasoma Perera, Akaki Ramishvili, E. H. Rickard, J. R. Sesel, B. L. Shapiro, D. H. Sutherland, S. E. Trickey, Roger Whitaker.

D.O.—Mirza Mubashar Ahmad, Young Hi Barnard, Alick Cameron, M. J. Chapman, Mahtabul Islam Choudhury, J. L. Colvin, S. I. Davidson, P. D. A. Durham, Jean R. Ellis, P. N. Gay, R. M. Ingram, Muhammad Aman Ullah Khan, W. M. Levy, F. R. Lippay, Una Merrill, D. H. Nixzaman, Margaret M. O'Connell, M. D. O'Riordan, G. G. K. H. Parsons, Gillian D. Paterson, Lakshmi Narayan Prasad, Suresh Prasad, Max Schaffer, Sikander, Birendranath Sinha, P. H. Smith, Tin Hlaing.

D.C.H.—Safia Muin Ahmad, Rafique Uddin Ahmed, M. R. Alderson, P. L. Aston, Ashis Banerji, Donald Barltrop, J. B. Benwell, Nirmal Chander Bhandari, Cynthia A. R. Bray, Jill M. Buddin, Maureen V. Burrage, Ann C. Butler, Sarah Capell, Anne J. Caro, M. A. Casson, Jocelyn O. P. Chamberlain, Hin-Wing Chan, J. E. Charlewood, Kandathil Mammen Cherian, Mary Cherian, Momota Chowdhury, B. S. Clarke, Priscilla A. Clark-Maxwell, R. H. L. Cole, G. Z. Cooper, Jean E. Cree, J. E. Cullis, D. C. Curtin, Zarina Deobhakta, Charmaine M. D'Souza, Barbara B. Dunlop, Nula M. Durcan, Ola E. P. During, G. H. Fowler, Pattiyage Kusuma Maria Gomes, Joan T. Graham, R. H. E. Grant, Doreen Greene, G. M. Hadjiminas, T. M. Hardiker, Pauline F. Haswell, Rita Henryk-Gutt, Sheilagh Hingston, Maureen J. Hodgson, L. P. J. Holt, Barbara K. Howells, Joan P. Ingham, Cheng Hing Ip, M. D. D. Jayamanne, Jane G. Jenkinson, Kasem Jitpatima, Winifred M. Jones, Jayant Vishnu Joshi, Anusuya Kalyanaraman, Hassenali Cassim Keshavjee, Amanullah Khan, P. J. Koblenzer, Elaine V. Laycock, Marian E. Le Couilliard, H. J. Liebeschuetz, E. C. De H. Lobo, R. D. Lockhart, Jane Lodwick, R. B. Lowry, Margery C. McKinnon, June M. McLeod, B. G. P. Macnamara, R. S. McWilliam, Nedumchalil Markose Mathai, Dante Mathuranayagam, P. K. Matthew, P. C. Matthews, Sharwan Kumar Mehra, Vengalil Narayani Menon, Anne C. Metten, W. R. Moore, J. G. Morris, Adewale Omololu, T. P. Ormerod, E. P. O'Sullivan, Freda M. Paul, Umsieruby Pillay, Thakur Baidyanath Prasad, Azima Iqbal Qureshi, Faizur Rahman, Juliet Saunthari Rajaratnam, Gwyneth Richards, Ethel A. Richardson, Gilliam P. Roach, Derek Robinson, Jean E. Rotherham, Jean Rowley, Elspeth M. Russell, Nasser Sabokbar, Anne Savage, J. W. Scopes, Doreen Set, Jagannath Sharan, J. S. Shepherd, Pamela M. Sherman, B. A. M. Smith, Frederick Smith, Uma Sreenivasan, J. P. Stanfield, G. M. Steiner, Tin U, A. J. M. Tudor-Hart, Tara Hari Vanarase, Shirin Abdulhussein Visram, Saiyid Abdul Wahid, Paul Wellings, J. L. Wilkins, Marian A. Wilkinson, Mary E. Wood, D. J. Woods, Trevor Woodward, H. J. Wright.

D.T.M. & H.—Abdul Sattar Abdul Aziz Abbasi, Syed Anees Ahmed, Ihsan Raouf Bahrani, W. B. R. Beasley, Madhukar Kishanrao Bedarkar, Elias Ivar Bengtsson, A. T. C. Bourke, Miroslav Crkvenac, Girish Chandra Das, Bhringeswar Deka, Bhimrao Dhole, C. G. B. Downie, F. Po Tun Fok, Bipin Harakhji Ganatra, R. G. B. Graham, Nicole C. Grasset, Abdol-Reza Hossein-Pour, B. D. J. Leary, Ake Mats Oskar Ljunggren, Francis Mills, Achyut Govind Motiwale, Humayun Mumtaz Husain, Subramaniam Nagaswami, Deb Narayan, J. L. Norquist, Ma Khin Thaung Nyunt, Nora V. O'Brien, R. H. Oram, Coimbatore Raghavendra Ramanathan, Premananda Roy, James Sharp, Nawal Kishore Prasad Singh, Boobpa Sri-Aroon, A. R. Taylor, Madhusudan Prasad Thakur, Tin Ohn, Kin Tint, Leendert Van Ieperen, Thomas Varughese, K. S. Warren, Dona Priyalatha Wijesinghe, R. R. L. Wild.

On Friday, April 24, at 4.30 P.M., at the college, Dr. J. H. Louw, professor of surgery, University of Cape Town, will

give a Moynihan lecture. His subject will be the pathogenesis and treatment of congenital intestinal atresia.

Faculty of Dental Surgery.—On Friday, May 22, at 5 P.M. at the college, Lord Cohen will give a Charles Tomes lecture on facial neuralgias. He will later open the department of dental science.

Hunterian Society

The subject for this society's 1959 essay competition is the Use and Abuse of Sedatives. The competition is open to all general practitioners resident within the British Commonwealth. Further details may be had from Mr. George Qvist, the hon. secretary, 72, Harley Street, London, W.1.

Society for the Study of Infectious Disease

This society will hold a meeting on Saturday, May 30, at 10.30 A.M. at Ruchill Hospital, Glasgow. Further particulars may be had from the secretary, Dr. J. B. Landsman, at the hospital.

European Society of Hæmatology

This society will hold a congress in London from Sept. 7 to 12. Further particulars may be had from the secretary, Dr. Ernst Neumark, department of pathology, St. Mary's Hospital, London, W.2.

International Association of Gerontology

The European clinical section of this association will hold a meeting in Nancy and Vittel from June 25 to 28. Applications should be sent before April 30 to Dr. E. Woodford-Williams, department of medicine and geriatric medicine, General Hospital, Sunderland.

Blood Club, Birmingham

A Blood Club has been formed in Birmingham to discuss at informal meetings problems of hæmatology and blood-transfusion. Details may be had from Dr. Elizabeth Topley, c/o Blood Transfusion Service, 15, Ampton Road, Edgbaston, Birmingham, 15.

Central Midwives Board

Mr. Arnold Walker has been re-elected chairman and Prof. A. A. Moncrieff deputy chairman of the board.

Courses for Hospital Administrators at Leeds

As part of the University of Leeds pilot scheme in hospital administration, a residential course for 9 secretaries and finance and supplies officers from the hospital service will be held from June 8 to 20. Other members of the course will include 2 senior Civil Servants, 1 local-government officer, 2 doctors, 2 senior nursing administrators, and 2 others. The theme will be possible developments in government and the social services over the next twenty years.

Electrical Techniques in Medicine and Biology

A conference on this subject will be held in Philadelphia from Nov. 10 to 12. Further particulars may be had from the conference secretary, Dr. D. A. Holaday, College of Physicians and Surgeons, Columbia University, N.Y. 32, New York, U.S.A.

Manchester Medical Exhibition

This exhibition will be held in the City Hall, Deansgate, Manchester, from Monday, April 27, to Friday, May 1. Sir Geoffrey Jefferson will open the exhibition on April 27 at 2.45 P.M. Further particulars may be had from the organiser of the exhibition at the City Hall.

International Medical Days of Verona

This conference will be held in Verona from Oct. 1 to 3. Further particulars may be had from the conference secretary, Istituti Ospitalieri, Borgo Trento, Verona, Italy.

Prof. J. N. Davidson is visiting Poland at the request of the biochemical committee of the Polish Academy of Sciences. He will lecture at the Universities of Warsaw and Cracow.

Dr. Enrique del Castillo, head of the endocrinology department at the Rivadavia Hospital, Buenos Aires, is visiting hospitals in this country at the invitation of the British Council.

The late Dr. A. R. Friel left £1000 to the Royal Free Hospital School of Medicine " for the assistance of poor women students ".

The Belmont Hospital Clinical Society will hold a meeting on Wednesday, April 22, at 5.30 P.M., when Dr. Elizabeth Tylden will speak on the role of the day hospital in community psychiatric care.

The Medical Electronics Discussion Group of the Institution of Electrical Engineers will hold a meeting at the Institution, Savoy Place, London, W.C.2, on Friday, May 8, at 6 P.M. Dr. D. H. Shinn and Dr. N. L. Lloyd will speak on microwave radiation hazards.

The United Hospitals Choir will give a choral and orchestral concert, in aid of the Imperial Cancer Research Fund, on Tuesday, May 5, at 8 P.M. at Chelsea Town Hall, London, S.W.3. Tickets (7*s*. 6*d*., 5*s*., 3*s*. 6*d*.) may be had from Miss E. Sorensen, South Western Hospital, Landor Road, S.W.9.

Diary of the Week

APRIL 19 TO 25

Monday, 20th

WRIGHT-FLEMING INSTITUTE OF MICROBIOLOGY, St. Mary's Hospital Medical School, W.2
5 P.M. Dr. D. A. L. Davies: Antigens of Pathogens.

Tuesday, 21st

ST. MARY'S HOSPITAL MEDICAL SCHOOL
5 P.M. Dr. C. N. Smyth: Membranes in Relation to Labour.
INSTITUTE OF DERMATOLOGY, Lisle Street, W.C.2
5.30 P.M. Dr. N. R. Mackay: Applied Physics. (First of two lectures.)
ROYAL ARMY MEDICAL COLLEGE, Millbank, S.W.1
5 P.M. Sir Howard Florey: Atheroma and Other Arterial Changes.
SOCIETY FOR THE STUDY OF ADDICTION
8 P.M. (11, Chandos Street, W.1.) Dr. H. Halbach (W.H.O.): Possibilities of Prevention of Drug Addiction. (Kelynack lecture.)
UNIVERSITY OF LIVERPOOL
5.15 P.M. (New Medical School, Ashton Street, Liverpool.) Mr. R. Guy Pulvertaft: Surgery of the Hand.

Wednesday, 22nd

POSTGRADUATE MEDICAL SCHOOL, Ducane Road, W.12
2 P.M. Dr. M. G. P. Stoker: Latent Virus Infections.
INSTITUTE OF DISEASES OF THE CHEST, Brompton, S.W.3
5 P.M. Dr. I. S. Longmuir: Aspects of Oxygen Transport.
ROYAL INSTITUTE OF PUBLIC HEALTH AND HYGIENE, 28, Portland Place, W.1
3.30 P.M. Dr. V. A. Lloyd: Problems of Child Development.
MANCHESTER MEDICAL SOCIETY
5 P.M. (Medical School, University of Manchester.) Dr. Macdonald Critchley: Kinesics, or the Doctrine of Gesture.

Thursday, 23rd

UNIVERSITY OF LONDON
5.30 P.M. (London School of Hygiene and Tropical Medicine, Keppel Street, W.C.1.) Dr. G. E. Palade (New York): Structure and Function of Blood Capillaries.
ROYAL SOCIETY OF MEDICINE, 1, Wimpole Street, W.1
8 P.M. *Urology*. Prof. C. E. Dent, Mr. D. R. Davies: Parathyroid Disease.
LONDON HOSPITAL MEDICAL COLLEGE, Turner Street, E.1
4.30 P.M. Dr. Robert Coope: The Changing Face of Respiratory Medicine. (Schorstein lecture.)
POSTGRADUATE MEDICAL SCHOOL
4 P.M. Prof. L. J. Witts: Medical Surveys and Clinical Trials.
INSTITUTE OF DERMATOLOGY
5.30 P.M. Dr. G. C. Wells: Benign Skin Conditions Requiring Radiotherapy.
ASSOCIATION OF SURGEONS OF GREAT BRITAIN AND IRELAND
9 A.M. (Royal College of Surgeons, Lincoln's Inn Fields, W.C.2.) Opening of three-day meeting.

Friday, 24th

ROYAL COLLEGE OF SURGEONS OF ENGLAND
4.30 P.M. Prof. J. H. Louw (Cape Town): Observations on the Pathogenesis and Treatment of Congenital Intestinal Atresia. (Moynihan lecture.)
UNIVERSITY OF LONDON
5 P.M. (University College Hospital Medical School, University Street, W.C.1.) Prof. D. E. Cannell (Toronto): The Maternal Mortality Committee and Obstetric Practice.
ROYAL SOCIETY OF MEDICINE
8.15 P.M. *Obstetrics and Gynæcology*. Prof. George Schaefer (Forest Hills): Treatment of Female Genital Tuberculosis.
POSTGRADUATE MEDICAL SCHOOL
10 A.M. Professor Louw: Carcinoma of the Thoracic Œsophagus With Special Reference to the Disease in the South African Bantu.
INSTITUTE OF LARYNGOLOGY AND OTOLOGY, 330, Gray's Inn Road, W.C.1
5.30 P.M. Mr. Wallace Black: Problem of Allergy.
MEDICAL SOCIETY FOR THE STUDY OF VENEREAL DISEASES, 11, Chandos Street, W.1
7.30 P.M. Dr. S. M. Laird, Dr. Eric Dunlop: Clinical Assessment of the Treponemal Wassermann Reaction.

Births, Marriages, and Deaths

DEATHS

HEATH.—On April 3, Philip Maynard Heath, M.S., F.R.C.S., of Little Croft, Fleet, Hants, aged 82.